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INFLAMMATION

AN ARTICLE BY J. G. ADAMI, M.A., M.D., REPRINTED FROM PROF. CLIFFORD ALLBUTT'S NEW SYSTEM OF MEDICINE

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PREFACE

Believing that it will be advantageous to the students attending my course to be able to obtain for themselves this study or essay upon Inflammation, I have begged the publishers of Professor Allbutt's *New System of Medicine* to grant me reprints, especially for the use of McGill students. I would here record my appreciation of the favour shown to me by The Macmillan Company in departing from ordinary usage and acceding so willingly to my request.

J. GEORGE ADAMI.

Pathological Laboratory,
McGill University, September, 1896.

INFLAMMATION[1]

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PART I. — A GENERAL SURVEY OF THE PROCESS OF INFLAMMATION

CHAPTER 1. — INTRODUCTION

Definition of Inflammation. — It is usual to begin the description of a morbid process by defining that process. In the case of inflamma-

[1] The following article is an attempt to bring into order the very numerous recent researches upon the inflammatory process, and to show whither they appear to tend; it pretends in no wise to be a complete treatise upon the development of our knowledge of the subject. Space alone has forbidden that I should trace the full history. I would therefore strongly urge that as a corrective other works be consulted in which the earlier theories are treated at length; more especially would I recommend (as throwing light upon the progress of our knowledge) Professor Burdon-Sanderson's article upon Inflammation in Holmes's *System of Surgery*.

tion, however, we have to deal with a process so complex, so modified by modifications of the many factors involved, and so variable in its manifestations according to the variety of its causes and the region of incidence, that the attempt to define it has proved a pitfall to pathologist after pathologist; moreover, to advance a definition of the process at the beginning of this article in terms differing to any considerable extent from those employed by previous writers, would demand a criticism of the many previous attempts; and in order that the definition put forward be duly supported, would necessitate an essay covering the whole field about to be traversed. I shall then leave definition to the end, until I have marshalled my facts, and have brought into line all that appears to me necessary for a correct understanding of the process. The definition must be the summing up of the subject, not the introduction thereto.

Use of the Name. — Yet, in the meantime, inasmuch as divergent views are held of the limitations of the use of the name inflammation, a few words of introduction are advisable.

Two courses are before us: either to employ the name strictly in accordance with the primitive definition, and thus only to include as cases of inflammation those states in which there are present redness, swelling, heat and pain, rigidly excluding all cases in which these cardinal symptoms are not present; or, on the other hand, departing from tradition, to include as inflammations all those morbid processes which seem to have a cause and progress inseparable from and merging into the cause and progress of the state characterised by the classical symptoms. The first course is impossible; it is as though one were to declare that red phosphorus is not phosphorus because in externals generally it does not agree with the definition of the yellow form made years before the allotropic modification was discovered. We are now well agreed that of the classical symptoms, one, two or three may be unrecognisable, and in fact absent; and yet the condition of inflammation be undoubtedly present.[1]

The second is the only possible course, that, namely, which associates all those states which under suitable conditions may result in the production of the four classical symptoms, and moreover originate from a common cause. Holding this view, it will in the meantime be well for me, in order to afford a starting-point for the description and discussion of the subject, to select from the many definitions one which is based not on symptomatology, but upon ætiology, and indicates a common origin for all cases of inflammation. I would select that which in this country has received the most cordial support, the definition given by Professor Burdon-Sanderson in his well-known article in Holmes's *System of Surgery*: "The process of inflammation is the succession of changes

[1] A course allied to this has found favour of late years among sundry surgical pathologists, who would limit the use of the term to those cases and those only in which the classical symptoms, or the majority thereof, are present and associated with suppuration,— they urge with Hüter that inflammation only occurs when pyogenic micro-organisms are present, and state that when a wound heals aseptically it heals without inflammation. This modified course is equally impossible; pyogenesis must not be confounded with inflammation.

which occurs in a living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality." This definition includes too much. The hæmorrhage that occurs in the liver when it is injured, and the changes that there occur in the extravasated red corpuscles, are scarcely to be classed among inflammatory phenomena; the atrophic changes which occur in the retina, when through injury it becomes detached, are due mainly to malposition and disuse rather than to the primary trauma. But, as Dr. Burdon Sanderson has pointed out, the definition has this great advantage, that stating the cause, it clearly recognises inflammation as a process and not as a state. The external manifestations of this process under favourable conditions — where the region injured is a loose and vascular tissue, and where the injury is sufficiently severe or extensive — are redness, swelling, and heat with pain: redness from the congestion of the vessels; swelling from the exudation of fluid and corpuscles from the congested vessels; heat from the increased amount of blood in the region, and pain from the pressure upon and irritation of the terminations of the nerves in the region. To these four symptoms may be added a fifth, disturbance of function brought about by this departure from the normal condition of the region. Under unfavourable conditions — where the region injured is dense or less vascular, or where the injury is less severe — one or all of these symptoms may seem wanting; nevertheless a minute examination of the tissues will show the same succession of changes as in the former case.

Chapter 2. — The Comparative Pathology of Inflammation

Accepting, then, this working definition, in order to arrive at a due comprehension of the succession of changes which we take to constitute the inflammatory process, it will be well with Metschnikoff[1] to institute a series of observations upon the reaction to injury exhibited throughout the animal kingdom from the lowest forms upwards to man. By this means we shall be enabled to determine what factors in the inflammatory process are from their constancy of primary importance; what are common and essential, and what are superadded in the higher animals.

The Response to Injury among the Protozoa. — Beginning our study with the lowest and simplest forms of life — forms so lowly that they have been regarded both as animals and as plants — we find even here phenomena accompanying the reaction to injury which throw light upon the inflammatory process as seen in the higher animals. Taking as an example the amœba, we find, in the first place, that the nucleus plays an

[1] The succeeding paragraphs are of necessity very largely an epitome of sundry portions of M. Metschnikoff's most pregnant work upon the comparative pathology of inflammation. By comparing them with the work in question, it will, however, be seen that they depart from it in several points; more especially in dwelling upon the extracellular activity of the wandering cells, and in bringing more prominently forward the response to injury on the part of the fixed cells.

important part in this reaction. If, as Metschnikoff has shown, one of the larger amœbæ be cut in two, the region of injury becomes rapidly indistinguishable — the protoplasm of each moiety closes up, leaving no mark or scar: but of the two parts that which retains the nucleus grows and proliferates; the other disintegrates in a longer or shorter time. Or injury may induce changes in the protoplasm of the entire amœba: thus, Miss Greenwood points out that, without necessarily bringing about death, the interrupted current or an aqueous solution of thymol leads to a process of exudation or extrusion of clear hyaline spheres, or of spheres holding crystals and granules, from the surface of the organism — a process resembling that occasionally seen in the cells of an inflammatory area in higher animals. Nor is this all; apart from changes in the structure of these unicellular animals, differences may be seen in the behaviour of amœbæ towards foreign bodies. It would seem, according to Le Dantéc, that amœbæ ingest non-irritating foreign substances indifferently, provided they be sufficiently small. Around each particle so ingested a vacüole is formed, and the fluid in this becomes increasingly acid, and at the same time digestive. Krukenberg, Reinke and Miss Greenwood have conclusively proved these and similar food vacuoles in the amœba and other Protozoa to contain a pepsine or digestive ferment, which, as Le Dantéc has shown by very delicate tests, exerts its action in an acid medium (the general protoplasm of the cell body being alkaline); this digestive process leads to the solution of food stuffs, preparing them to be taken up by the protoplasm of the organism. If the foreign substances be incapable of digestion they are sooner or later extruded. It is by this formation of digestive vacuoles that the amœba acts upon and destroys bacteria, diatoms, and other microbes ingested by it. There are, however, microbic forms around which it would seem that no proper vacuolation is developed, or if developed, the acid digestive fluid is neutralised by substances discharged from the parasites; where this is the case, instead of destruction there is continuance of vitality and actual multiplication of the invading or parasitic form, leading to the eventual death of the amœba. Metschnikoff has observed this chain of events in one of the amœbæ which ingests and becomes the host of a minute rounded form, the Microsphæra. Phenomena of like nature may be observed among the ciliate and flagellate infusoria. While these phenomena may primarily be regarded as the method employed by the Protozoa for the assimilation of food stuffs, they also are clearly the means whereby the Protozoa defend themselves against living organisms which have gained entrance into them, and thus form the reaction to possible injury; for when in certain cases the means of defence are overcome, the parasitic organisms gain the upper hand and lead to death.

There is yet another reaction to injurious influences exhibited by the Protozoa into which it is necessary that I should enter at some length. This is exhibited by the amœba, but can be and has been most fully investigated in the myxomycetes — multicellular forms which

can with equal propriety be classed as animals or plants, although usually they are included among the latter. These organisms form large plasmodia (masses of protoplasm, that is), in which, under ordinary conditions, the nuclei are the only indication of the individual cells which by their fusion have formed the masses. They are to be met with in leaf mould, and on the surface of moist decaying wood over which they creep with an amœboid movement; and inasmuch as they may attain great size — some species attaining twelve inches or more in length — they form admirable material for biological study.

Ten years ago Stahl, investigating one of these myxomycetes (the *Æthalium septicum*, an organism found in tan pits), showed that if placed upon a moistened surface close to a drop of infusion of oak bark, the plasmodium moved actively towards and into the infusion; if placed similarly near to a solution of glucose (0·5 per cent) it moved with equal rapidity away, and so also in the case of solutions of various salts. These observations of Stahl were (if we except Engelmann's observations in 1881 upon the tendency of sundry bacteria to remove from regions poor in oxygen to those where oxygen is present in abundance) the first of a series of observations upon the attraction and repulsion of plants and portions of plants by chemical substances. To this property Pfeffer, who has made the fullest series of studies upon it, has given the name of chemiotaxis, in place of Stahl's narrower "trophotropism"; and one speaks of a positive or a negative chemiotaxis according to the attraction or repulsion exerted. If, as Metschnikoff has pointed out, the advancing edge of one of these plasmodia (of Physarum) be injured by cauterisation, the region of injury dies; the protoplasmic currents, which had been advancing, reverse themselves abruptly, and within an hour the plasmodium has moved away, leaving the débris of the destroyed region behind. These experiments are so simple, and the results obtained seem so natural, that it may be asked whether it be worth while to attach a name to this property of living matter. Yet the name is in itself an aid to bearing these properties in mind; and, as will be pointed out later, the recognition of them is of material help in solving certain of the difficulties that present themselves in the study of inflammation in the higher animals. Among these myxomycetes another fact can be made out. Stahl observed that the plasmodium of Fuligo, which at first moves away from a two per cent solution of common salt, will after a time (more especially if it has suffered from lack of water) adapt itself to the solution, advancing its pseudopodia or protoplasmic processes into it. With other myxomycetes the same adaptation has been observed. That is to say, by use or adaptation a negative may be transformed into a positive chemiotaxis. To this change I shall have occasion to revert.

The Response to Injury among the Metazoa. — Passing from the Protozoa to the Metazoa, we reach immediately (or almost immediately) a series of beings in which the division of labour among the cells has led to the development of three cell layers — an outer ectoderm, an inner endoderm, and an intermediate layer of mesoderm.

Even in the very lowest forms among the Metazoa it is noticeable that of these three layers there is one, the mesoderm, whose cells have the especial function of reacting when any irritant or injurious stimulation is applied to the organism. Taking what are perhaps the simplest forms in which to observe the relationship and properties of these layers, Metschnikoff has studied these results of injury in the larval forms of astropecten and other echinoderms. At one well-recognisable stage these larvæ resemble little more than the gastrula stage of the embryologist; the endoderm or hypoblast appears as a cul-de-sac — an invagination of the ectoderm or epiblast — while the mesoderm is represented by amœboid cells, budded off from the endoderm, lying or floating in the semiliquid substance filling the general body cavity. The ectoderm is so delicate that any sharp substance can readily penetrate into the body cavity; and, when this happens, it is noticeable that the wandering mesodermal cells make their way to the foreign body, attach themselves to it, and fuse into plasmodial masses, thus forming a wall, as it were, around the invading substance, and cutting it off from the general body system. Here, then, in an organism possessing neither nervous nor vascular system, the reaction to injury, where that injury has not been sufficiently intense to cause destruction of the outer layer of cells, is simply and solely confined to the wandering cells of the body; there is no effusion of fluid; there is not necessarily phagocytosis on the part of these cells; any digestive and destructive action on their part — any attempt in this way to remove the foreign body — must then be by excretion, *by extracellular action*. At the same time, this fusion of the cells and formation of a plasmodium around foreign substances of greater diameter than the individual mesodermal cells may be looked upon as a mechanism whereby the equivalent of intracellular digestion is gained. But, as among these low forms cases occur in which, without the formation of plasmodia, the cells perform their destructive action upon bodies of larger size than themselves we do not lack examples of what must be considered as excretory destructive powers on their part. That these cells in the echinoderms are also capable of destroying minute foreign bodies by intracellular action, that is, by phagocytosis, has been demonstrated in the larger transparent larval form known as Bipinnaria Asterigera; on introducing bacteria under its ectoderm the mesodermal cells are seen to approach, and by their long pseudopodia to adhere to and ingest the still living motile bacteria, which are rapidly digested.

Besides this reaction to injury on the part of the mesodermal cells, a further response is exhibited to a remarkable degree among the lower Metazoa — I refer to the great power of regeneration of lost parts, of cell proliferation leading to the reproduction of destroyed regions. This power is best seen in the classical example of the Hydra, which may be cut into many pieces, each one of which is capable of growing, so that in a relatively short time it becomes a fully formed individual. It is interesting to note in relation to the frequent tendency towards hyperplasia and excess growth following upon injury in

the higher animals, that among low forms, such as Hydra and Cerianthus, the same tendency is yet more strongly marked. Thus, as Loeb points out, if an incision be made in the stem of a Hydra, a whole new oral pole, provided with tentacles, will branch out from the region of cell destruction. In the actinian Cerianthus the process is not quite so extensive; yet from the lower lip of the lateral incision a set of tentacles develops in all respects similar to those around the mouth.

Ascending to the Worms, we find that the protective agency devolves upon mesodermal cells suspended in the perivisceral fluid, and again forming the peritoneal endothelium. We arrive, that is to say, at a state in which a lymphatic system may be said to be present; for the spaces in which the free corpuscles lie are strictly homologous to the lymph-containing spaces of the vertebrate organism, and these corpuscles may be regarded as lymph corpuscles; the peritoneal endothelium corresponds with the mesodermal peritoneal endothelium of vertebrata.

Among the annelids the process of reaction to injury may be well followed in the earth worm by studying the sequence of changes that occur around the gregarines which infest the male genital organs. While these parasites are active by their movements they prevent the adhesion of the wandering cells; but so soon as they pass into the resting stage antecedent to spore formation, the cells form a thick mass around them. The parasite on its part forms a thick cyst wall; nevertheless, it may not unfrequently be observed that, despite this protection, the parasite changes its appearance under the action of the surrounding plasmodium, and in fact is killed. While this is happening no change could be detected by Metschnikoff in the neighbouring blood-vessels; these appear to remain completely inactive: no exudation is noticeable nor any recognisable change in volume.

While among the Worms a well-developed and closed vascular system is not unfrequently present, in other animal forms, which in most respects present a much more complex and advanced development, namely, in the Arthropods and Tunicates, this is not the case. In these the blood pours from the tubular heart sooner or later into the lacunæ of the general body cavity; and whether veins be absent (as is most usual), or present (as in the Cephalopods), the blood is sucked back from the body cavity into the heart. This incomplete circulation, interesting as it is in connection with the development of the vertebrate circulation, is interesting also from the fact that its incompleteness in these large and wide-spread classes of animals prevents reaction to injury from being associated with vascular changes. The blood in these animals, circulating through the ramifications of the body cavity, is evidently a mesodermal fluid, if it may be so termed. Its corpuscles are clearly mesodermal; and without going into full details as to the properties of these corpuscles, it may be said that they represent an interesting series of stages in the subdivision of labour. For example, as Mr. Hardy has shown us in a low form of crustacean like Daphnia (the

water flea), but one form of cell is present, whereas in the highly-developed Astacus (the cray fish), there are three distinct forms of leucocytes (no red corpuscles being present), each of which appears to have distinct functions. The one form in Daphnia has the property of taking up fat globules and food particles from the alimentary tract, foreign particles, such as granules of carmine or Indian ink, and the spores of parasites (Monospora, Metschnikoff); it is granulated, containing minute spherules which stain with basic aniline dyes (basophile granules), and under certain circumstances it may be seen to explode with lightning-like rapidity. In the higher Astacus there are in the circulating hæmal fluid two varieties of cells: one is extraordinarily explosive; when removed from the body cavity it gives off fine blebs or vesicles of its substance with such rapidity that, unless the greatest care be taken, nothing is seen of the cell save its nucleus; this form is phagocytic: the other form is far more stable, and is loaded with large spherules which have a great affinity for acid dyes — they are eosinophilous — may be actively extruded, and undergo decomposition; these cells never act as phagocytes. The third form, with basophile granules, is rarely found in the blood, and then only as the result of special stimuli; but it is present in considerable numbers in the peculiar tissue which forms a sheath around certain of the arteries — Haeckel's "Zellgewebe;" this form is phagocytic, and can be seen to contain globules of ingested fat.

As Metschnikoff demonstrated, in his most remarkable study upon a disease of Daphnia caused by the entry of the spores of a yeastlike organism (the Monospora) into its body cavity, its one form of leucocyte can be seen to react swiftly towards the spores; the cells approach them, form a plasmodium around and eventually digest and destroy them. If, on the other hand, in consequence of their great numbers or the relative paucity of the leucocytes, certain of the spores be not attacked and develop uninterruptedly into mature torulæ, the leucocytes show no tendency to approach them — in fact, their neighbourhood leads to the explosion of the leucocytes — and the torulæ, multiplying, lead to the death of the organism. Often, again, brown eschars may be recognised upon the transparent carapace of a Daphnia, due to injuries by other individuals; beneath these scars are to be found masses of leucocytes which remain in the region of injury until the cells of the tissue have proliferated, and there is complete union and repair.

In addition, then, to the immediate reparative and protective reaction of the leucocytes, there is exhibited among the higher invertebrata a later reaction in the shape of proliferation of the fixed cells. This proliferation, while not so extensive as among the lower invertebrates, can nevertheless be very great; and cells of all forms, whether of hypo-, meso- or epiblastic origin, and tissues so highly developed as the muscular and nervous, may participate in it. In illustration of the ample power of tissue reproduction after injury possessed by these animals, I need but mention the trite examples of the reproduction of the hinder segments

of divided worms, and in crustaceans the restoration of injured and cast off claws and appendages.

Many more instances might be given to show that the reaction to injury remains essentially a reaction on the part of the wandering and fixed mesoblastic cells of the organism, followed in sundry cases by proliferation of the fixed epi-, meso- and hypoblastic cells, and by repair where these have been destroyed. Although these arthropods, molluscs and tunicates have a vascular system, yet, inasmuch as this is open, its changes, if they occur, could scarcely modify the inflammatory process.

The Response to Injury among the Vertebrata. — If now we pass to the vertebrates, the picture presented is far more complex: not only do these present a highly-developed nervous system, but, moreover, the blood is enclosed in a complete vascular system. We shall now consider at length the results of an injury of an organ in one of these higher animals.

Chapter 3. — The Main Forms of the Process of Acute Inflammation in the Higher Animals

The Experimental Production of Inflammation in Non-Vascular Areas. — Let us begin with the succession of changes that occurs in the simplest case, namely, *in a non-vascular area, in one of the lowest vertebrate forms* — for instance, in the embryonic axolotl ten to fifteen days old; let us curarise it, and apply a minute crystal of silver nitrate to the side of its flattened transparent tail fin, washing away the remains of the crystal with salt solution; or again, we may pass into the tail a small needle filled with finely-powdered carmine. By either procedure a certain number of cells is destroyed. The neighbourhood of the injury now becomes swollen (it may be by imbibition of water through the wound), and the surrounding cells tumefied, vacuolated and less refractile. This is the *first stage* — that of injury and modification of the surrounding tissue. In a little time a few wandering cells (leucocytes) approach the injured region; by the next day these are present in fair numbers, and can be seen to have taken up the particles of carmine or débris of the destroyed tissue. This is the *second stage* — that of immigration of leucocytes. There are no vessels in the transparent fin of these young axolotls, no dilation of those nearest to the fin, and no diapedesis. All the leucocytes that pass to the part are pre-existing wandering cells of the connective tissue, — a fact of some little importance in connection with the origin of certain of the pus cells in the suppurative process of higher animals. The *third stage* is that of repair, of proliferation of the injured epithelium, return of the fixed cells of the tissue to their previous state, and emigration of the wandering cells. A very similar progress of events occurs if the experiment be repeated upon the tail fin of the young newt. The same rapid alteration in the large branched connective tissue cells (which become vacuolated as their

long processes are drawn in and shortened), and the same immigration of motile cells from the surrounding connective tissue are to be seen; but here we now find the earliest evidence of vascular participation, for, according to Metschnikoff, complete arrest of the circulation may occur in the nearest vascular loop. By the next day the parts have returned to the normal condition.

If from these cases we pass to mild inflammatory disturbances affecting the non-vascular regions of animals far higher in the scale, we again discover a like process of events. For this purpose *the cornea* affords an excellent opportunity; in health it is absolutely non-vascular; it is perfectly transparent, and is so thin that it can readily be examined microscopically.

The cornea of mammalia, and indeed of vertebrates in general, is formed of fibres which run in layers parallel to the surface. These fibres, while roughly arranged side by side and parallel to one another in any given layer, are placed at an angle to the fibres of the layers above and below. Although free from blood-vessels the cornea is far from being devoid of channels along which lymph freely passes. Between the several layers there exist spaces in which lie the flattened connective tissue cells of the organ; and, by means of numerous fine channels, these spaces around the cells are connected with similar spaces lying anteriorly, posteriorly and laterally. Through this rich anastomosis of channels there is a free flow of lymph. These channels are really continuations of the body cavity of the animal; they represent, and in fact play the same part as the single body cavity of such a simple form as the larva of Astropecten, while the cells lying in the spaces are mesoblastic cells which have become fixed.

Few studies are better calculated to impress the investigator with a sense of the depth of the well at the bottom of which truth lies, than a research into the abundant literature dealing with observations upon the stages of the inflammatory process as it occurs in the cornea, and with the deductions therefrom. One after another the adherents to successive forms of inflammatory belief have found in experiments upon this simple tissue ample support for their particular creeds.

Selecting from among the many observations those which have stood the test of time, I will begin with the simplest, and pass on to those dealing with an increasing intensity of the inflammatory process.

If, as Senftleben first pointed out, the centre of the cornea of a rabbit be washed with a strong solution of zinc chloride, then, in favourable cases, although the epithelial covering be gravely injured, there may be no actual rupture of the outer layers of the tissue. Such a cornea removed twenty-four hours later may show no sign of migration of leucocytes — no sign, again, of congestion of the vessels at the periphery. The only indications of injury and reaction may be the destruction of the corneal corpuscles immediately beneath the cauterised area, and the appearance of a zone surrounding this in which the corneal corpuscles appear enlarged, distinct and tumefied. The process may

continue and advance insensibly to repair without the intervention of leucocytes; the hypertrophying cells of the "granular" zone eventually undergoing karyokinesis, and thus by multiplication replacing the corpuscles destroyed.

Here, then, necrosis and new growth of the fixed cells of the tissue are the only recognisable factors in the process of repair of injury. It must be confessed that the conditions permitting this simplest form of reaction are of rare occurrence; it is worthy of attention that they can exist.

By a slight modification of the preceding conditions another factor may be brought into play. If, after cauterisation in the manner above described, a break be made into the cauterised surface; or if again, without cauterisation, a little of the corneal tissue be removed, then in a few hours a small whitish opacity is to be noticed within the corneal tissue in the immediate neighbourhood of the break in the continuity, and upon examination this opacity is found to be due to a massing of small round cells. As there is at this moment no sign of proliferation of the connective tissue cells of the cornea, these newly-collected cells can only be leucocytes; and further examination of their properties proves them to be such: there is, however, no evidence of dilation of the peripheral vessels, no indication of diapedesis through their walls. The leucocytes, therefore, can only have entered into the wound from the cornea itself and from the conjunctiva and the lachrymal fluid bathing it. In this experiment the inflammatory process is represented by destruction of tissue and immigration of leucocytes, followed by repair; neither the vascular nor the nervous system play any part in it. We are forced to the conclusion that the leucocytes have massed themselves in the injured area purely on their own initiative; and that there must be an attraction, a chemiotaxis or chemiotropism, leading them actively to approach the region of cell destruction.

The observations made upon these two simple cases help us materially to understand the series of events which occur in more intense inflammation of the cornea, such as that produced by injuring the surface and causing the entrance into the injured region of a small quantity of a pure culture of the Pyococcus aureus. This may be accomplished by injecting the culture into the centre of the healthy cornea by means of the needle of a Pravaz syringe (Jacobs). The micrococci so introduced grow rapidly, the growth so extending along the lymph spaces that a branched mass of the microbes is produced, having the spot of inoculation as centre. Around the growth as it extends may be seen a sharply-marked area in which the corneal corpuscles show evidences of degeneration; the nuclei stain faintly, and the corpuscles, speaking generally, have a shrunken appearance. Here, again, the first effect of a microbic, as of a simple chemical injury, is to bring about degeneration of the fixed cells of the tissue. Within eighteen hours the zone of proliferating cocci and cell degeneration is well marked; and now the second stage begins to be clearly manifest, namely, the determination

of leucocytes to the seat of injury. Within twenty-four hours there is a dense packing of these corpuscles around the central degenerated area, and great numbers of leucocytes may be seen converging along the lymph spaces from the periphery of the cornea. This is the second stage of the process, the first stage of reaction to the injury inflicted by the invading micro-organisms. If, as by Cohnheim[1] in his original experiments upon the injury to the cornea, more careful examination be made into the stages of the determination of leucocytes, it can be seen that this determination is closely related to changes set up in the vessels at the periphery of the cornea; they become more prominent, the region has a congested appearance, the smaller as well as the larger vessels are dilated, and there is abundant evidence that the leucocytes are passing out from the contained blood into the surrounding lymph spaces. Indeed the accumulation of leucocytes shows itself first at the periphery of the cornea near the vessels, and gradually approaches the region of injury. Into the mechanism of this diapedesis, and into a fuller description of the changes that take place in the blood-current in these distended vessels, I shall enter later when discussing the changes in highly vascular regions. Suffice it to say here that no distinction can be made out between the behaviour of the leucocytes in the previous experiment, when they entered the wounded area from the external surface, and in this where the majority find their entrance from the blood; as in the previous case the part played was evidently active, so must it be here also. We cannot arrive at any other conclusion than that some attractive force leads to their determination towards the inflammatory focus. As we can easily show, by repeating the experiment, many of these leucocytes take up and contain numerous cocci, while other cocci remain free in the tissue spaces. Many of the leucocytes degenerate and present a broken down appearance; and, as at the same time an increasing area of the corneal tissue becomes disintegrated, an ulcer appears. According to the virulence of the culture and the reaction on the part of the organism, the process may now extend, a larger and larger portion of the corneal tissue becoming affected; or, on the other hand, there may be an arrest of the progress, the massing of the leucocytes preventing, as a barrier, the further extension of the micrococci into the lymph spaces;[2] while at the same time there is an advance of newly-formed capillary vessels into the previously non-vascular tissue. It is to be noticed that the blood-vessels at the periphery of the cornea are prominent and dilated, and from them fine new vessels with very delicate walls pass towards the injured region. At the same time many of the corneal corpuscles, outside the area of destruction, can by appropriate staining be seen undergoing mitosis and proliferating. Thus the active repair of the tissue is initiated.

[1] There can be no question that Cohnheim in his experiments induced not a simple keratitis but one which in the absence of aseptic precautions rapidly became septic and suppurative.

[2] Into the details of this action I shall enter more fully later.

The Experimental Production of Inflammation in Vascular Areas. — From this study of inflammation, as it occurs in a region devoid of blood-vessels, let us now pass on to the more complicated process of inflammation in vascular areas; and, as in the previous case we considered an ascending or advancing series of reactive changes, so here let us begin with the slightest injury associated with the mildest reaction, and pass onwards to states in which the inflammatory manifestations are more and more pronounced.

If an incision be made with a perfectly aseptic instrument into the skin, also rendered aseptic, and be so made as to divide the dermis and tissues immediately below, without at the same time injuring any large vessel, it is the common experience of modern surgeons that repair takes place with the minimal amount of change recognisable as inflammatory. Repair takes place indeed so rapidly that, if the divided structures have come or have been brought into immediate contact, there may be firm adhesion at the end of twenty-four hours. This is *primary union*, or union by first intention, which, rare in the old days, commonly occurs in this era of aseptic surgery. The full sequence of events in these cases cannot, it is true, be well determined by continuous microscopic examination; but if the rabbit or dog be employed, and tissues, wounded in the manner described, be removed and examined at successive short intervals, we see that the changes which occur are mainly, nay almost entirely, related to the pre-existing cells of the part. The section divides a certain number of capillaries; but in the very act of division the divided walls are apparently brought together; and, partly by this means, partly by contraction, the lumina of these minute vessels become occluded, and the hæmorrhage into the wound is altogether inconsiderable. Within an hour after the operation it is evident to the naked eye of a careful examiner that the immediate neighbourhood of the wound is slightly reddened and tumefied, but only very slightly; and, associated with this, there is a feeble exudation between the apposed surfaces. But the exudation is not great, and even within this first hour after the infliction of the wound there may be development of fibrin and coagulation of the exudate, leading to the formation of a provisional cementing together of the opposed surfaces. In this exudation, and in the tissues in the immediate neighbourhood, the leucocytes that have undergone diapedesis may be few and far between, and may scarcely attract attention. The reaction, then, on the part of the vessels and of the leucocytes is of the slightest. Study of sections shows that the main rôle is played by the pre-existing cells of the part; of these a certain number (not so many as might *à priori* be expected) are destroyed immediately, and show all the signs of disintegration; a number relatively large have been injured only, their nuclei remaining intact, though their processes or some portions of the cell bodies have been cut through. It is difficult to determine these injuries in the small cells of the cutaneous tissues; they are better seen in the peritoneum when slight inflammatory changes have there been

induced. This, however, can be made out that the cells in the immediate neighbourhood of the wound became enlarged, and, without showing signs of division, prolong themselves (that is to say, send out prolongations) into the region of the provisional fibrinous cicatrix. In this way, before the end of the second day, there may be a more or less complete replacement of the primary unorganised cementing substance by organised growing tissue, — formed, in the first place, by the interlacing of processes from the neighbouring cells; in the second, and later, by a multiplication of these cells, together with a development of new capillaries, few in number, which branch off from the slightly-congested vessels in the neighbourhood. Thus in this case the process of repair is characteristically associated with hypertrophy and the new growth of the fixed cells of the tissue; while vascular changes, exudation and leucocytosis, are relatively little marked. I have, however, never come across a case in which they have been entirely absent, save when the section has been truly extra-vascular — that is to say, when it has not penetrated into the vascular region of the skin, and has affected only the epidermis and outermost layers of the dermis. In such cases the response to injury may show itself purely as a proliferation of the epithelial cells.

As I have said, observations of the above nature labour under the disadvantage that they must of necessity be discontinuous. I bring them in at this point, inasmuch as they represent the mildest condition of the inflammatory reaction. I have not personally observed this series of changes in tissues which permit of continued study under aseptic conditions; neither am I acquainted with any observations wholly fulfilling these conditions — made, that is to say, upon transparent vascular tissues subjected to the mildest aseptic injury and examined continuously under the microscope.

The response to injury in the cases just mentioned was of the slightest. Let me now pass on to cases in which it becomes more pronounced; and in order to continue the comparative study of inflammation I would first describe the series of *events in a highly vascular and transparent region* in a low vertebrate animal, namely, in the tadpole's tail. If this be injured, either by the application of a caustic or by the introduction of a foreign inert body into its substance, a definite advance upon what was recognisable in the case of the axolotl, for example, is to be made out. Here the tail is very vascular, the wandering cells of the connective tissue are very few in number, while the blood is fairly rich in leucocytes which are small relatively to the size of the vessels. The results of injury are a congestion of the vessels, noticeable within fifteen minutes, and a well-marked determination of leucocytes to the injured region. These cells, in the main, pass out from the vessels; the few leucocytes pre-existing in the tissue appear to play a very small part. Compared with the axolotl experiment this observation is of considerable interest. Instead of a slight reaction slowly developing there is a rapid reaction; instead of a slight accumula-

tion of leucocytes there is a most pronounced accumulation. If there be any meaning in the determination of leucocytes to the region of injury, then evidently the active participation of the vessels of that region in the reactive process is fraught with benefit — it is a further important factor developed with the development and advance of the organism.

The fuller details of this vascular interference in the inflammatory process have been followed by many observers, among whom first and foremost was Cohnheim; and to this end the frog has supplied the most convenient means in regions at once vascular and fairly transparent, such as the web of the hind feet, the tongue, and the mesentery. Other observers passing higher in the scale of vertebrates have employed the mesentery of the cat, dog, and other mammalia. Suffice it to say that, with slight modifications due to local conditions in the tissue examined rather than to the animal selected, the process has been found to present the same features throughout the whole of the adult vertebrata, from the reptilia upwards. For general examination, perhaps, the best and simplest method of observing the succession of changes that follow injury of a vascular area is to be found in what I believe to be Coats' modification of Cohnheim's original experiment upon the frog's web (Coats' *Pathology*, 1889, p. 119). In order to reproduce as nearly as possible the conditions of an ordinary wound, instead of employing a caustic or chemical irritant, a small portion of the cutaneous surface is nipped off — the section being just deep enough to pass through the cutaneous layers without causing hæmorrhage. For the experiment to proceed satisfactorily, it is necessary that the frog be curarised after having been pithed. The web of a small frog is so thin that the changes occurring in and around the vessels of the part can readily be followed even with a high power of the microscope.

The first change noticeable in the immediate neighbourhood of the injured membrane is a dilation of the vessels, first of the arteries and then of the veins; and in this first phase there is a very evident acceleration of the blood flow. At this early period the capillaries show little evidence of dilation, but in the course of an hour expansion is readily distinguishable, and sundry capillary channels, previously invisible, become occupied by blood and show themselves. This first stage lasts for an hour, or in some cases perhaps two, and is followed by a phase of slowing of the blood current. While previously a well-marked axial stream of corpuscles had been evident, with a peripheral zone of plasma devoid of corpuscles, the former now broadens out, the latter becomes less and less, and as it narrows an increasing number of the clearer rounded hæmal leucocytes are to be seen in it travelling at a slower rate than the more axial stream, and every now and then stopping beside the walls of the vessels, and after a short stoppage passing on again. The leucocytes conduct themselves as if they have become "sticky."[1]

As the current becomes yet slower all distinction between axial and

[1] Even so low down in the scale as Daphnia this same peculiarity is noticeable: there in health, as Hardy has pointed out, the leucocytes move freely; but, if the slightest injury be

peripheral streams is lost; the corpuscles, closely packed together, fill the whole lumen; the leucocytes in increasing number approach the vessel walls; they adhere more firmly, and so long as a current is recognisable the action of the stream leads them to assume a pear-shaped appearance, the rounded ends pointing in the direction of the current.

As the stream slows gradually the corpuscles may move at last in a series of jerks synchronous with the heart beats; or frequently in the veins and capillaries the mass of blood may be seen moving slowly first in one direction, then in the other. Frequently one or other of these stages is followed by complete stagnation or stasis of the blood in the vessels of the injured area—I say frequently, for at other times little or no absolute arrest is seen in the vessels. Accompanying this stage, although observers employing other and chemical methods of inflicting injury have in general omitted to call attention to the fact, there is already a considerable oozing or exudation of clear fluid from the wound; there is, that is to say, an outpouring of lymph, and that apparently from the distended vessels. Now, with the slowing of the stream the leucocytes, accumulated next to the walls of the small veins and within the capillaries, pass from the interior to the exterior of these vessels; and, if the process be studied carefully with a higher power, it can be seen that this mode of passage is of an active, or apparently active nature.[1] A series of leucocytes can be distinguished some of which are rounded or flattened in immediate contact with the wall of the vein; others possess a prolongation passing into the wall; in others, again (or in the former if they be watched in the fresh specimen), the prolongation enlarges on the outer side of the small vessel while the portion of the leucocyte within the vessel becomes smaller. The final phase of this act of diapedesis is that the whole leucocyte passes through, and is found in the lymph spaces around the vessel wall. This process of diapedesis may be so general that in the course of five or six hours all the small veins of the region show a crowd of leucocytes situated along their outer surface. With these a greater or less number of red corpuscles may also make their escape.

Although the capillaries, from the very smallness of their diameters, do not show the so-called "margination" of leucocytes, nevertheless this same process of diapedesis may occur at various points along their course, so that outside the capillaries also a fair number of the same small highly-refractile cells endowed with amœboid movements can be observed.

In this modification of Cohnheim's experiment a further stage is to be recognised. While at first the fluid exuded was clear and relatively free from cells and cell débris, now, as the inflammatory process continues, an increasing number of leucocytes is contained in the exudation. The

inflicted upon the carapace, the leucocytes, previously unadhesive, soon show the tendency to adhere to the walls of the body cavity beneath the region of injury and elsewhere.

[1] The process can be fully made out if at this stage the wounded region be removed, fixed immediately in weak osmic acid, and prepared for examination by the higher powers of the microscope.

leucocytes do not remain in the immediate neighbourhood of the vessels, but many of them pass on to the injured surface; still it would seem by active amœboid movement. Thus at the end of six hours this surface may be covered by a serum or fluid in which are great numbers of these leucocytes. Here then we have the first step towards the formation of a scab or provisional protective covering to the wound.

Further observations cannot well be carried out in the pithed and curarised frog; but if an unpithed, non-curarised animal be taken, and the observations upon the earlier stage be neglected, it can be made out that if irritant matter do not find entry into the wound the process may be arrested at this point; the leucocytes upon the surface may break down, and with their breaking down and the formation of fibrin a soft scab be formed: the stasis of the blood in the distended vessels may be followed by a re-establishment of the current and slow return of the vessels to their former calibre, while beneath the thin, soft scab the epithelial cells rapidly proliferate. Within twenty-four hours there may be abundant evidence of this new growth of the epithelium tending to encroach upon and cover the wound. At the same time the region becomes less and less populated with leucocytes, so that — not to enter fully at this point into the reparative process — within sixty hours the region may show little sign of the injury and consequent inflammation.

On the other hand, if irritants of a microbic nature enter the wound the process may extend, as in inflammation of the cornea. More especially if the water in which the frog is kept become foul, there is a tendency in the inflammatory processes to spread; and in the cells of the central area, both fixed and migrated, to break down, leading to the formation of a spreading ulcer. The steps of this sequence of affairs it is difficult to follow by continuous microscopic examination, partly on account of the increased opacity of the region, partly because the process extends over days rather than hours. Here, therefore, I merely mention this possible extension of the change with its main naked-eye appearances.

It is not possible by continuous observation to make out the steps of this more extensive inflammation characterised by excessive emigration of leucocytes and destruction of these together with the fixed cells of the tissue — the pyogenetic inflammation. Several observers, however, have followed its successive stages by means of examination of affected tissues at successive intervals after the infliction of injury.

The Experimental Production of Suppurative Inflammation. — While, as shown by Councilman, Grawitz and de Barry, Straus, Leber and others, a suppurative inflammation may under certain conditions be brought about experimentally by the action of chemical irritants, such as mercury and turpentine; yet under ordinary pathogenic conditions suppuration is induced by the growth of micro-organisms within the tissues. Hence it is better to study the conditions as induced by the inoculation of pus-producing microbes into one or other tissue. A very full series of observations upon the development of abscesses through the agency of the Staphylococcus pyogenes aureus has been made by Hohn-

feldt. He employed rabbits, and inoculated small quantities of pure cultures of the microbe subcutaneously.

Four hours after inoculation the vessels of the region were found densely filled with corpuscles, and in them a commencing margination of the white corpuscles was discernible. Leucocytes were present within the tissue in numbers greater than normal; although, compared with later stages, they were infrequent. They were of two kinds—the mononuclear in the majority, the polynuclear (or more truly the form with polymerous nucleus) in lesser numbers; both forms were congregated mainly around the line of entrance of the injecting needle. Many of the connective tissue cells were so swollen as to be rounded rather than flattened. The injected cocci, lying in the lymph spaces, were scattered through the tissue; in part free, in part already ingested by cells, not only by the leucocytes, but also by connective tissue cells: the number within leucocytes was not inconsiderable.

Preparations made at the end of ten hours showed the same conditions, but more distinctly. There was ample evidence of migration of the leucocytes, margination in the congested vessels, various stages of passage through the vascular walls, and large collections of the cells in the perivascular lymph spaces; from these they spread into the spaces between the bundles of connective tissue fibrils. The cocci lay in the lymph spaces and were increased in number, and the massing of leucocytes corresponded in position to the accumulation of microbes. In these regions the leucocytes were mainly polymerous or multinuclear, but in the boundary zone away from the cocci the uninuclear form predominated.

At the end of twenty hours there was further accentuation of these conditions. As yet an abscess proper had not formed, but enormous numbers of leucocytes were present, and also of micrococci; the fibrillæ of connective tissue were widely separated by the collections of leucocytes, and these cells clustered round and hid the connective tissue cells.

With the completion of forty-eight hours a well-defined abscess had formed, separated sharply from the surrounding healthy tissue. The centre of the abscess was seen to consist of densely-packed leucocytes mingled with large growths of cocci. These leucocytes were almost entirely "multinuclear;" and in this central area the nuclei of some showed fragmentation. Neither leucocytes nor connective tissue cells showed the slightest indication of mitosis. In the central area all traces of the previous capillaries had disappeared; in the peripheral zone they were easily recognisable, being fully injected and showing a marginal disposition of their leucocytes, many of which could be seen (in osmic acid preparations) fixed in the process of diapedesis.

The majority of the cocci lay in these leucocytes. Even where the colonies of the microbes were thickest there the majority were intracellular. Passing towards the periphery the number of cocci became smaller and smaller. At the periphery they could be seen not only to be intracellular, but also free in the lymph spaces; and Hohnfeldt, with other observers, saw them definitely grouped within the endothelial cells

of the peripheral vessels. Thus it may be noted that at this stage the proliferating microbes extended into the healthy tissues outside the abscess.

In the centre of the abscess the original tissue had wholly disappeared; nearer the periphery light streaks and bundles of the disintegrating fibrillæ could be recognised between the leucocytes.

Not till about the tenth day did new growth of tissue begin to show itself. During the preceding six days there had been more breaking down of the polynuclear leucocytes, characterised by fragmentation of the nuclei and by fatty degeneration of the cell substance. But by the tenth day the periphery had begun to assume the appearance of granulation tissue; it contained numerous capillaries and new-formed connective tissue with characteristic epithelioid cells or fibroblasts possessing large oval pale staining nuclei. In these cells, as in the connective tissue cells of the surrounding healthy tissue, could the numerous steps of indirect cell division be made out. In this granulation tissue cocci were absent and leucocytes were infrequent. In the soft, cheesy central area masses of cocci were still present. Whether these were living or dead Hohnfeldt did not determine; he inferred (what has since been proved by several observers to be an unsafe inference) that inasmuch as they stained well with aniline dyes they were alive.

Thus, to sum up Hohnfeldt's observations, the processes occurring in a suppurative inflammation that ends in healing are the following: —

1. Congestion of the region of invasion, with margination of the leucocytes.
2. Collection, in the region, of uninuclear leucocytes; then diapedesis of leucocytes with polymerous nuclei: multiplication of the cocci.
3. Ingestion of large numbers of the microbes by the polymerous leucocytes and other cells, including the endothelial cells of the vessel walls.
4. Increasing immigration of leucocytes until the tissue becomes densely packed. This is accompanied by a yet greater proliferation of the microbes, which extend (*i.e.* are carried by lymph streams or by cells) into the region outside the developing abscess.
5. Destruction of the tissue of the affected part.
6. Degeneration of the leucocytes within the sharply-defined abscess.
7. Eventual proliferation of the connective tissue at the periphery of the abscess; formation of fibroblasts in the highly vascular surrounding zone; cicatrisation and encapsulation of the débris of the leucocytes and micrococci.

There are not a few points in connection with these observations of Hohnfeldt that deserve discussion; very possibly he has misinterpreted certain of the appearances seen by him. On the whole, however, he draws a full and accurate picture of the successive stages of suppurative inflammation, and I may defer discussion to a later review of the action of the leucocytes and of the formation of fibrous tissue respectively.

However, before leaving this general description of the series of

anatomical changes induced by injury, there is another phase of the inflammatory process set up by pathogenic micro-organisms which must not be passed over — I refer to those cases in which, instead of ending in repair, there is *extension and generalised disease*. The stages preceding extension vary with the nature of the microbe; thus, in some cases, the reaction to the invasion of the microbe is mainly leucocytic (as with inoculations of the micrococci of suppuration), in others it is mainly exudative or serous, the congestion of the vessels being followed by abundant exudation of serum into the tissues. This is the case in inoculation of animals — such as rabbits, guinea-pigs and fowls — with cultures of micro-organisms which are peculiarly virulent in their behaviour towards these animals. Such a serous or exudative inflammation is, for instance, well seen if the vibrio Metschnikovi be inoculated into the pectoral muscles of a fowl. Within twelve hours, it may be, the seat of inoculation becomes greatly swollen, and on section is found reddened and congested; while from it drains an abundance of relatively clear, faintly-reddish serum containing but a few leucocytes.

In such a case as this the micro-organisms appear to pass with ease from the centre of infection into the surrounding tissues, and thence into the lymphatics and general circulation, whence they may be obtained within twenty-four hours. Where there has been a well-marked abscess formation in the region of invasion there, as already indicated, it is true that the microbes may be found outside the abscess at a fairly early period; but, in the main, proliferation is limited to the abscess, and the blood remains free and sterile. Under certain conditions of great virulence of the pyogenic microbes it is found that as the abscess extends it becomes ill-defined — there is no sharp demarcation between the collected leucocytes and the surrounding tissue; the columns of leucocytes spread indefinitely from the centre, and numerous micrococci are intermingled with them. Where this is the case there is a marked tendency for the microbes to find their way into the general circulation from this irregular peripheral extension along the lymphatic spaces, and to set up a condition of septicæmia as in the more serous inflammation described above.

Septicæmia, or the passage of micro-organisms into the blood, with all the results of such a passage — the condition which sundry French observers have described as inflammation of the blood — is dealt with in another article. In septicæmia we pass beyond the local response to injury, we deal with a state of general systemic disturbance. Nevertheless certain phases of the septicæmic condition throw light upon the inflammatory process.

In the first place, it is of interest to note that when the infective micro-organisms and their products are within the vessels they fail to induce the cardinal symptoms of inflammation. They do not lead to exudation of fluid from the blood or to wide-spread diapedesis of leucocytes. The stimulus, whatever it be, which leads to these phenomena at the point of invasion is no longer called into activity when the noxa is

within the circulatory apparatus. This is the reverse of what might be expected if the inflammatory process were primarily due to a modification of the endothelium of the vessel walls by the irritant, a modification passively permitting the exudation and passage outwards of the leucocytes.

The statement that infective micro-organisms and their products circulating within the blood fail to induce inflammatory changes, would seem to need modification when the development of *metastatic abscesses* is taken into account. But a study of the mode of production of these abscesses shows that the statement still holds. Such abscesses originate round emboli of pyogenic micro-organisms in the capillaries. Sundry cocci are arrested in the capillary, proliferate and fill the vessel. It is only when a minute vessel is thus occluded that the abscess process begins, that is to say, when by this occlusion the vessel has become extravascular; and while it is true that, primarily, the arrest of pathogenic microbes within the capillaries is often associated with a small accumulation of intravascular leucocytes and with degenerative changes in the vascular endothelium, the metastatic abscess, as such, forms not by accumulation of leucocytes in the occluded vessel, but around it; the leucocytes emigrating from surrounding capillaries.

Inflammatory Fever. — In the second place, through this study of advancing inflammation it is of interest to trace the very close relationship that exists between inflammation and fever. Besides the local changes here described, local injury is accompanied by systemic disturbances. These may be slight or grave.

Take, for instance, progressive abscess formation, or follow the development of a malignant carbuncle in man. At first the reaction is purely local, but very soon, long before any of the micro-organisms are capable of detection in the blood, there is exaltation of temperature and a slight febrile state, the fever becoming more and more evident as the local process becomes more and more extensive, until with the detection of the microbe in the blood the most severe fever, with constitutional disturbance, sets in. Local inflammation, then, without any other possible explanation than either the nervous irritation to which it may give rise, or the passage into the general circulation of the soluble products of bacterial growth and tissue destruction, or both, may lead to the development of the febrile state. How large a share is played by these two possible factors it is difficult to say. That bacterial products injected into the circulation lead to the rapid production of the febrile state we have ample evidence; but whether these act directly by inducing increased cellular activity, or indirectly by stimulating the cerebral centres, we cannot absolutely say. As yet we have little accurate knowledge of the parts played by the nervous system in the development of the febrile state. This, however, may safely be declared, that the more we study the continued fevers the more do we discover that these commence by a local inflammatory disturbance. The continued fevers are the continuance, or rather the extension, of a primarily localised inflammatory lesion. [*Vide* art. on "Fever."]

Summary of the Facts thus far brought forward.

The main facts gathered thus far concerning the inflammatory process, and the conclusions to be drawn therefrom, may now be placed in order before I discuss in detail the various factors in the process. They are —

1. Injury, when it is not so widespread and severe as to lead to the death of the individual, is followed by a reaction on the part of the organism.

2. In unicellular organisms the continued vitality of the individual after injury, and in multicellular organisms the vitality of the individual cells, are dependent primarily upon the persistence of the nucleus; if this be destroyed or removed the rest of the cell is incapable of complete restitution and continued growth.

3. In unicellular organisms the reactive process is twofold, and consists of (*a*) destruction or removal of the irritant; destruction being brought about by a process of intracellular digestion, removal by extrusion of the irritant: (*b*) new growth of the organism.

4. This response to injury on the part of unicellular organisms is essentially reparative.

5. In multicellular organisms, with division of labour among the constituent cells of the individual, there is a separation of functions; the twofold reaction to local injury is yet more clearly marked; but

(*a*) The destruction or removal of the irritant is *in the main* accomplished by the wandering cells of mesoblastic origin.

(*b*) The new growth to replace the tissue destroyed by the irritant proceeds *in the main* from the fixed cells of the tissue.

6. Ascending the scale of multicellular organisms, a division of labour and differentiation of function is discoverable among the wandering mesoblastic cells. Whereas in the lower forms of the Metazoa one type of leucocyte alone is present, in the higher forms two or more varieties can be distinguished which possess different properties and act differently towards irritants introduced into the system.

7. According to the nature of the irritant causing the injury, the leucocytes are actively attracted in greater or less numbers to the region of injury, surround the irritant, and remove or destroy it by means very similar to those employed by unicellular organisms. Where the irritant is present in the form of discrete particles, there some at least of the leucocytes may incorporate the particles, and remove them or destroy them by a process of digestion. Others of the leucocytes in the higher Metazoa never act thus as phagocytes; nevertheless they are equally attracted to the focus of inflammation, and presumably tend to counteract the irritant by some other (extracellular) means.

8. While to the wandering cells appears to be allotted the main duty of removing deleterious and irritant matters, certain of the fixed cells of the organism, notably the endothelial cells of the vessels, can also exert these functions.

9. Among the very large number of Metazoan forms in which no complete vascular system is present, this attraction of the leucocytes to the region of injury is at first the sole response to injury. At a later period proliferation of the fixed cells occurs in the neighbourhood of the injury.

10. Among the higher Metazoa, in which there is a well-developed vascular system, the determination of leucocytes to the region of irritation still continues, and is in fact markedly aided by the participation of the vessels in the inflammatory process.

11. The vascular phenomena in inflammation may be regarded as serving two main purposes — (*a*) the pouring out of increased fluid into the injured area; (*b*) the afflux and diapedesis of leucocytes.

12. Even in the highest Metazoa, possessing fully-developed vascular systems, the response to injury in a non-vascular area, such as the cornea, may be associated with no change in the surrounding vascular areas, but purely with a determination to the injured area of leucocytes already free in the surrounding tissues.

13. The second phase of the inflammatory process, that of tissue repair, but very rarely occurs without evidence of previous migration of leucocytes and exudation from the congested vessels.

14. A comparative study leads inevitably to the conclusion that the determination of leucocytes to the region of injury is the most constant and most characteristic early response to injury recognisable throughout the Metazoa, and that it must be regarded as the most important factor in the first stage of the inflammatory process. The vascular phenomena noticeable in the higher Metazoa must be regarded as a second and highly important factor of later development and adjuvant. New tissue formation is the prominent characteristic of the later stages of the process.

15. As among the Protozoa, so in the Metazoa, the response to injury is consistently an attempt to repair the injury.

This general survey of the response to injury throughout the animal kingdom demonstrates most clearly that the same broad principles, the same methods of defence and repair on the part of the organism, are called into activity from the lowliest forms to the highest; that, in fact, no line can be drawn to separate one set of phenomena as truly inflammatory from another set which, while also a response to injury, are non-inflammatory. Although it is true that the term inflammation implies a reddening and congestion of the vessels, we find upon closer examination that this reddening and congestion is not the fundamental but a superadded feature in the process of repair of injury — a feature superadded as the organism advances in its place in the animal kingdom. Thus if we are to comprehend the process satisfactorily we must pass beyond the narrower acceptation of the term.

Having thus sketched broadly the general phenomena of the inflammatory process, it will be well now to describe in fuller detail the factors of this process among the higher vertebrata, and to bring together the

more important results of the study of the respective functions of the wandering cells, the vessels, the fixed cells, and the nervous system in inflammation.

PART II. — The Factors in the Inflammatory Process

Chapter 1. — The Part played by the Leucocytes

The Leucocytosis of Inflammation. — As I have already shown, there is more than one form of leucocyte in the mammalian organism, and the several forms evidently possess different attributes, and act differently in the reaction to injury. Inasmuch as these forms have been variously classified — so variously, in fact, that it is often far from easy to collate the various descriptions, and to discuss the forms distinguished by one observer in the terms of another — it is necessary to give the chief classifications of them, and their relations.

The first to discriminate between the forms of white corpuscles in the blood was Wharton Jones so long ago as 1846. He drew a distinction between

A. Granule cells { Finely granular. / Coarsely granular.
B. "Nucleated" cells — Non-granular.

His observations, together with those of Rindfleisch in 1861 and 1863, were confirmed and advanced by Max Schultze, who made out the following forms: —

1. Small round cells with round nucleus and little clear protoplasm.
2. Larger cells with round nucleus and more clear protoplasm.
3. Cells with finely granular protoplasm, and one, two, or more nuclei.
4. Cells with coarse granules in the protoplasm.

The distinctions drawn were, so far, purely morphological; and very little notice was taken of these varieties for a long period until Ehrlich, in a notable series of papers extending from 1878 to 1887, drew attention to the fact that the wandering cells of the organism react diversely towards the different aniline dyes and possess diverse tinctorial affinities indicating chemical differences in the nature of certain constituents of the cell bodies. The granules of the previous observers were found to be variously affected by the dyes employed; they were shown not to be fatty, but — as Ehrlich put it — of the nature of a glandular excretion;[1] and comparing the effects of the two groups of aniline colours — that in which the dye is associated with the acid constituent of the salt, and that wherein the dye forms the base (the "acid" and "basic"

[1] J. Weiss has studied the micro-chemical reactions of the eosinophilous granules, and concludes that they are of albuminoid nature; as they were found not to be digested in gastric juice he would ally them with the nucleins.

aniline dyes respectively) — he made out the existence of five forms of granulation associated with as many varieties of wandering cells. His table of cells according to their granulation is as follows: —

α. Granulation — Eosinophile. — Cells frequently in horse's blood, present constantly in small numbers in human blood; numerous in medulla of bones of rabbits, dogs, guinea-pigs, etc. Stain deeply with acid aniline dyes. Granules large and coarse.

β. Granulation — Amphophile. — Cells frequent in rabbits and guinea-pigs in blood; present also in medulla of bones. Stain both with acid and basic dyes. Granules fine.

γ. Granulation — Basophile. — Large cells found in the connective tissue, from the frog upwards, "Mastzellen"; in blood of man only in certain cases of Leucæmia. Stain only with basic dyes. Granules coarse.

δ. Granulation — Fine Basophile. — The "mononuclear" leucocyte of human blood. Granulation fine. Stain with basic dyes.

ε. Granulation — Neutrophile. — The most frequent leucocyte of human blood, "polynuclear." Stain only in neutral dyes — not in acid or basic.

While Ehrlich and his pupils, and Rieder, have done much to throw light upon the relative numbers of the leucocytes possessing these different granulations in different diseases, they have accomplished little in discovering the origin of the various forms, their functions, or their relationships. We owe the first satisfactory studies upon the properties of the different forms to Metschnikoff, who, at an early period in his long-continued and wonderful series of researches upon Phagocytosis, made out that the different wandering cells of the body act differently towards microbic and other foreign particles introduced into the organisms. Thus he was led to draw a distinction between —

1. Lymphocytes — immature leucocytes.
2. Large hyaline cells, mononuclear, phagocytic, "macrophages."[1]
3. Smaller neutrophile cells, polynuclear, "microphages."
4. Eosinophile leucocytes — not phagocytic.[2]

Quite recently the admirable researches of Prof. Sherrington, and of Dr. Kanthack and Mr. Hardy, have appeared which, starting on the groundwork laid down by the older observers, have made a notable advance in the determination of the function of the various forms of wandering cells in inflammatory and other conditions. The observations

[1] While acknowledging that a certain amount of convenience attends the employment of these terms, "macrophage" and "microphage," I cannot but agree with Professor Burdon-Sanderson that they are utterly barbaric.

[2] While this article was passing through the press, M. Mesnil, a pupil of Metschnikoff, has stated that eosinophilous cells can occasionally act as phagocytes. The statement is contrary to Metschnikoff's previous observations and, I may add, contrary to general experience. Until further confirmatory observations have been made, I am not prepared to accept the statement.

of Kanthack and Hardy are especially full, and I shall have occasion to refer continually to their results. In the meantime it may be said that they materially simplify the classification given by Ehrlich, by dividing the leucocytes thus: —

1. Coarsely granular } Oxyphile cells. Staining with acid dyes.
2. Finely granular }
3. Coarsely granular } Basophile cells. Staining with basic dyes.
4. Finely granular }
5. Hyaline cells.
6. Lymphocytes.

Their coarsely granular oxyphile cells are the eosinophile cells of most writers; their finely granular are the neutrophile and amphophile of Ehrlich. They prove conclusively that Ehrlich's neutral stain is in no sense to be regarded as such, but must be considered as an acid dye.

It is now possible to collate these various classifications, and in this way to begin to study the functions of the various forms with a clear appropriation of the terms employed in the following paragraphs.

Collation of the different Classifications of the Varieties of Leucocytes.

Kanthack and Hardy.	Ehrlich.	Metschnikoff.	Max Schultze.	Wharton Jones.
Lymphocyte.	Lymphocyte.	Lymphocyte.	Small round cell I.	Non-granular nucleated cells.
Hyaline cell.		Macrophagocyte.	Large round cell II.	
Coarsely granular oxyphile.	Eosinophile cell.	Eosinophile cell.	Cells with coarsely granular protoplasm.	Granule cells, coarsely granular.
Finely granular oxyphile.	Neutrophile, Amphophile } cells.	Microphagocyte.	Cells with finely granular protoplasm.	Granule cells, finely granular.
Coarsely granular basophile.	Basophile cell with γ granulation. Mastzellen.			
Finely granular basophile.	Basophile cell with δ granulation.		Cells with finely granular protoplasm.	? Granule cells, finely granular.

Lymphocyte. — Immature leucocyte; round nucleus deeply staining; scanty protoplasm; increased in number after food; diminished after starvation; indistinguishable from small elements of lymphoid tissue. Not phagocytic; variable in number; not amœboid; may form up to 30 per cent of the leucocytes present in human blood.

Hyaline Cell. — Round or kidney-shaped nucleus of slight staining power; abundant protoplasm; hyaline; non-granulated; actively amœboid and phagocytic; rare in blood (2 per cent); abundant in cœlomic fluid. Nuclei have been seen to undergo mitosis.

Coarsely Granular Oxyphile. — Large horseshoe-shaped nucleus (in man); relatively large spherules in protoplasm; highly refractive; staining deeply with acid aniline dyes; abundant in cœlomic fluid, in serous cavities, in inter-

stices of areolar tissue (K and H), and in bone marrow (Ehrlich); rare in blood (2–4 per cent); amœboid; non-phagocytic.

Finely Granular Oxyphile. — Smaller than last (in man); nucleus branching or polymerous, staining deeply; granules very small and spherical; feeble oxyphile reaction (Ehrlich's amphophile reaction in rabbit, neutrophile in man, etc.). Abundant in blood (20–70 per cent of all leucocytes); absent from cœlomic fluid; actively amœboid and phagocytic. The most common form of pus cell.

Coarsely Granular Basophile. — When found free in cœlomic fluid, round nucleus staining very feebly; spherules large and numerous, stain with basic dyes — somewhat similar cells are found stationary in connective tissue spaces — absent from human blood in health; non-phagocytic.

Finely Granular Basophile. — Spherical; smallest of the wandering cells; trilobed nucleus; clear cell substance containing great numbers of fine basophile dots. Found in human blood in small numbers (1–5 per cent); increased after meals.

From this description of the character of the various forms of leucocytes (for which I am largely indebted to Kanthack and Hardy) it will be seen that certain forms are characteristically present in the circulating blood, namely, the finely granular oxyphile and the finely granular basophile; others in the body fluid, namely, the coarsely granular oxyphile and coarsely granular basophile; while the lymphocytes and hyaline cells are common to both fluids. It must be added that the eosinophile, or coarsely granular oxyphile, are also present in small numbers in the healthy human blood: it occurs in larger numbers, however, in diseased conditions which do not come within the scope of this article.

Of the origin and relationship of these diverse cells we still know very little. As Gulland has pointed out, the blood of the embryo is entirely free from white corpuscles. The exact period at which each form makes its first appearance has not yet been studied, although in all probability such a study would throw a flood of light upon the origin of the different orders of cells.

The most that we can say with fair certainty is that the lymphocytes, while representing the larval form of leucocytes in general, are in the main derived from lymphoid tissue; that some of them develop into the hyaline cells (for, as Sherrington and others have noted, every gradation is observable between these two forms); and that what appears to be an immature eosinophile cell can often be detected in the peritoneal fluid, as also an immature coarsely granular basophile cell (Kanthack and Hardy). Beyond this we have not at present advanced.[1] Ehrlich's suggestion that the eosinophile cells are derived from the bone marrow may

[1] I quite understand that sundry observers regard all the various forms of leucocytes as modifications one of another. It is true that all embryologically have the same origin; so, for example, have the corpuscles of cartilage and bone, yet this does not make cartilage and bone one tissue. Everard, Gulland, Ruffer, Demoor and Massart, state that all transitions are observable between the various forms; I cannot but think that the methods of staining employed by these observers were insufficient for these wide conclusions. It is interesting to note that these observers, like Kanthack and Hardy, found Ehrlich's amphophile and neutrophile cells to stain with eosin, *i.e.* to be oxyphile.

be partially true, but not entirely; inasmuch as it is difficult to correlate the preponderance of these cells in the body fluid with so special and local an origin. Nor can the recent observation of Siawcillo, that eosinophile cells are abundant in the ray which possesses neither bone nor bone marrow, be regarded as favourable to Ehrlich's hypothesis. And again, the observations of Metschnikoff and his pupils render it eminently probable that some, at least, of the large hyaline cells are derived not from lymphocytes, but from proliferating endothelial cells of the lymph and blood-vessels and of serous surfaces. Finally, it is noticeable that the cells with multilobate nucleus (the finely granular oxyphile), the commonest of the hæmal leucocytes, are not to be recognised in lymphoid tissue: yet, as Sherrington has pointed out, certain of their peculiarities, notably the contorted shape of the nucleus, may be regarded as acquired, inasmuch as if they be allowed to remain at rest in the living state outside the body the nuclei become more spherical.

Of these varieties of wandering cells not all have, so far, been found to bear a part in the inflammatory process: but certain forms appear to have distinct functions therein: these are the finely granular oxyphile (neutrophile), the coarsely granular oxyphile (eosinophile), and the hyaline cells.

A word should here be said concerning the cells of later development, appearing as a result of inflammation — giant-cells, Ranvier's cells, and Gluge's corpuscles. Of these the last are evidently leucocytes of the hyaline type which have taken up the fatty products of tissue degeneration; the second — colossal cells breaking down with great ease — are of doubtful origin. Giant-cells would seem to be of more than one variety: some appear to be due to aberrant cell growth, wherein the nuclei undergo division without the protoplasm of the cell body following suit. The characteristic giant-cells of tuberculosis and chronic inflammation may now be said with fair certainty to be plasmodia, in all respects comparable to the masses of fused cells seen to form in the lower animals around foreign bodies, and by Kanthack and Hardy around masses of bacteria in the lymph of frogs outside the body. The recent observations of Borel and of Duenschmann strongly support this opinion.

Phagocytosis. — In the case of a very large number of pathogenic micro-organisms (so large a number that merely to enumerate them, with the names of the observers and of the animals upon which the observations have been conducted, makes a list so long that in the bibliographical table at the end of this article I give only the more important references, and not nearly the complete list), after inoculation into the organism, a very considerable proportion are to be discovered, sooner or later, within wandering cells which have collected in the region of inoculation. I have already mentioned more than one case of this nature in discussing the comparative pathology of inflammation. Evidently under certain conditions one of the functions of certain of the leucocytes is to attack and incorporate bacteria. The leucocytes having these properties are more especially the finely granular oxyphile (where the injection has

been into a neighbourhood richly supplied with vessels), the hyaline cells chiefly where the microbes have found an entry into the body cavity. It is, for instance, the finely granular oxyphile cell which is found in overwhelming numbers in an extending subcutaneous abscess, and these are seen to contain great numbers of the micrococci.

The conditions leading to this phagocytosis have been very fully worked out by Metschnikoff. He has amply demonstrated that the microbes can be taken up in a living condition. Thus, if the Vibrio Metschnikovi (a form closely allied to the cholera spirillum) be inoculated into the anterior chamber of the eye of an immunised animal, within a very few hours phagocytes are discovered filled with the small, slightly curved vibriones. If now one such cell be isolated, placed in a drop of

Fig. 1. — Resolution of acute infectious disease (relapsing fever), spleen pulp of monkey (Macacus erythr.), showing (*a*) microphage, multinuclear, with incepted spirochaetes; (*b*) solitary, and (*c*) forming dense tangle, (*d d*) nuclei of splenic tissue (Zeiss, $\frac{1}{12}$ ocular 4; × 1515 diam.). — [Metschnikoff (51).]

broth upon a coverslip, made into a hanging drop preparation and examined under the microscope, it is seen that the broth causes the death of the leucocyte; while with time, and favourable temperature, the microbes proliferate rapidly, and completely fill the corpuscle until it disintegrates; whereupon they proceed to multiply in the surrounding fluid. This seizing and incorporation of microbes does not then necessarily lead to their death. In certain cases of acute disease there may be abundant phagocytosis, and the disease progress nevertheless; the phagocytes being destroyed by the products of the incorporated organisms. This is the case in mouse septicæmia, in swine erysipelas, and (as has been shown quite recently by Gabritchewski) in diphtheria. As M. Roux remarks: "Ils ont fait de leur mieux en englobant les microbes, mais ceux-ci se sont adaptés au milieu intérieur des cellules, et ils ont triomphés." [1]

[1] Roux. — *Trans. Internat. Congress of Hygiene*, London, 1891, ii. p. 120.

In other less acute diseases, such as gonorrhœa; and in chronic maladies of a tubercular nature—in tuberculosis, leprosy, and glanders—the bacilli may in certain stages be found within the cells and rarely free in the lymph spaces, they appear to be almost parasitic, after the manner of the microsphæra previously referred to as infesting the amœba.

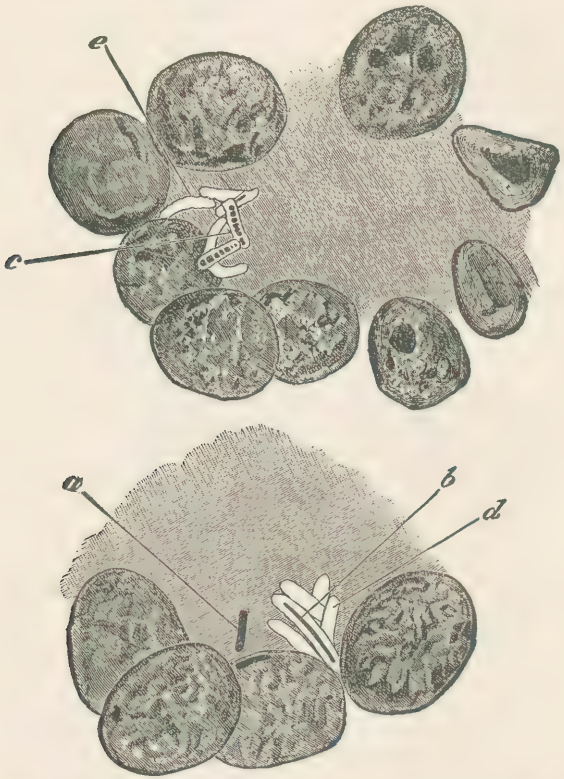

FIG. 2.—Two giant-cells, seen under high magnification (× 1515 diam.) from a rodent, the spermophile, inoculated with tuberculosis, to show stages in the destruction of the bacilli. *a*, unaltered bacillus; *b*, bacillus staining badly, and with greatly thickened capsule; *c*, bacillus granular and breaking up; *d e*, "shadows."—[Metschnikoff (51).]

In these cases it would seem as though the toxic properties of the microbes and the antagonising powers of the cells were nearly balanced. In tuberculosis, for instance, it is not unusual to find in the giant-cells some bacilli which evidently are undergoing degenerative changes, staining poorly and irregularly, or but faintly traceable as unstained, translucent shadows, while elsewhere they are apparently proliferating despite their intracellular position.[1]

[1] It is, however, unsafe to declare in all cases that because a micro-organism continues to stain well therefore it was living at the moment the preparation was taken and

And this equality, or almost equality of the resisting powers of cells and microbes, may explain the chronic nature of the diseases above mentioned. Nevertheless, in general, it may be stated that there is some relationship to be recognised between the amount of phagocytosis and the virulence of the microbe; the more virulent the microbes the less the proportion of them taken up by the cells; and, as Kanthack and Hardy have pointed out, the longer the time before the phagocytes come into action. As is the case in the unicellular organisms, so in the wandering cells of higher animals the process of destruction of the included microbes can, under suitable conditions, be seen to be digestive. Several observers have seen the anthrax bacillus, in frogs and other animals, wholly or in part surrounded by a vacuole developed within the leucocyte; and, as an evident result, the

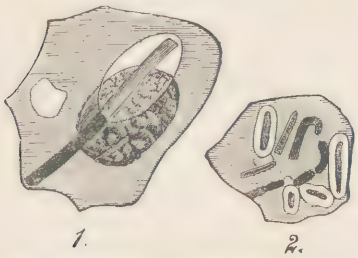

FIG. 3. — Phagocytes, macrophage and microphage, to show stages of digestion and destruction of bacilli, from spleen and eye respectively of white rat with anthrax. In *1*, part of the bacillus is unaffected, but a vacuole has formed around the other part, which further has now lost the power of taking the stain. In *2*, various stages are seen, the bacilli passing through the granular badly staining, to the vacuolated unstained, until finally but faint "shadows" are observable (Zeiss $\frac{1}{18}$, oc. 3). — [Metschnikoff (51).]

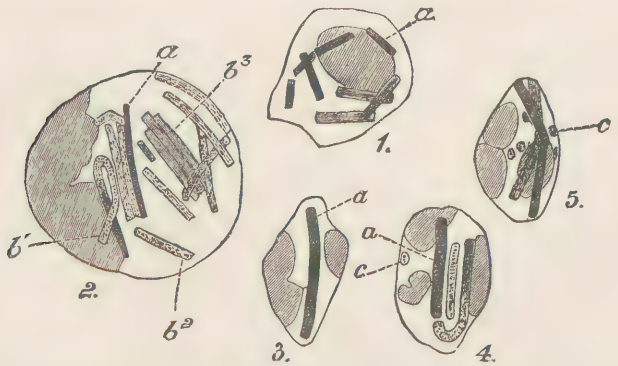

FIG. 4. — Anthrax of pigeon (an animal but slightly susceptible to the disease) to show stages of destruction of bacilli by phagocytes. *1* and *2*, macrophages: *1*, from exudation from eye of refractory bird; *2*, from muscle of region of inoculation of bird that succumbed; *3*, *4*, *5*, microphages — all from eye twenty-seven hours after inoculation; *a a*, unaltered bacilli; b^1 b^2 b^3, bacilli becoming more and more degenerated and indistinct; *c c*, débris of bacilli (Zeiss $\frac{1}{18}$, ocular 3). — [Metschnikoff (51).]

portion so surrounded has been seen to become swollen and fainter when stained, until it has undergone a veritable digestion and dissolution.

As with the lower organisms, so with the wandering cells of

fixed by heat. Thus in pneumonia after the crisis a fair number of diplococci may be found within the leucocytes of the expectorated contents of the alveoli, and these may stain perfectly well; yet it may be impossible to gain a single growth of the diplococcus from the same material.

the higher, there is an evident attraction, or chemiotaxis, whereby these cells pass towards the microbes and their products; and this chemiotaxis would also seem in general to be in the inverse ratio of the virulence of the microbes. I say in general, for with chemiotaxis as with phagocytosis there appear to be exceptions to any uniform law; and cases can be brought forward — of diphtheria, for example — in which the leucocytes, instead of being repelled, are attracted in great numbers to the region of inoculation of a most virulent bacillus.

The chemiotactic properties of the wandering cells have been especially studied by Pekelharing, Leber, Massart and Bordet, and by Gabritchewski.

Of the results obtained by these observers the most important are that leucocytes are variously attracted towards various substances. Thus Leber found that the introduction into the system of finely-powdered copper and various compounds of mercury caused an abundant collection of the wandering cells around the particles, while powdered gold, silver and iron exerted no such attraction. Gabritchewski and A. Schmidt showed that the products of bacterial growth in general possessed chemiotactic properties yet more powerful than simple chemical compounds. While the degree of positive chemiotaxis is found to vary within wide limits, the examples brought forward of negative chemiotaxis exerted by bacterial products have so far been very few — so few as to support the contention of Dr. Kanthack, that it is very doubtful whether any microbes by their products actually repel the leucocytes, though they are capable of causing the rapid destruction of the attracted leucocytes, and so of rendering the area around the microbes relatively free from wandering cells.

A very good study of the action of bacteria of different degrees of virulence can be made by repeating an experiment of Metschnikoff. The rabbit is an animal susceptible to the growth within its tissues of the bacillus of anthrax. As is well known, there are various means whereby the virulence of this microbe can be diminished; so that if cultures of the "attenuated" bacillus be inoculated into susceptible animals, these, instead of causing a fatal disease, induce but a transient local inflammatory disturbance, accompanied by fever, and followed by complete recovery. If now a small quantity of a virulent culture of the bacillus be inoculated into the one ear of a rabbit, and an equal quantity of an attenuated culture into the other, the results are very instructive. Within twenty-four hours it can be noticed that an acute inflammation has been induced in both ears; in both the vessels round the seat of inoculation are greatly congested, but whereas at the seat of inoculation of the virulent organism there is a serous inflammation so intense that the skin is raised and separated from the subjacent tissues by a clear, transparent, reddish fluid which also infiltrates the deeper tissues, in the other ear there is not nearly the same amount of swelling and serous exudation; the region of inoculation is more opaque and solid. Upon more minute examination the serous fluid in the first ear is found to

contain relatively very few leucocytes; the firmer mass in the second is composed of a huge aggregation of leucocytes [*vid.* art. "Anthrax"].

Evidently, therefore, the relative number of leucocytes migrating, and the quantity of serum exuded, depend very largely upon the intensity of the irritant; and by the intensity of the irritant, and the behaviour of the leucocytes, the forms of the inflammatory process may be classified.

But to the subject of classification I shall refer later. In the meantime it is well to sum up the theory of phagocytosis as upheld by Metschnikoff and those who see in this phenomenon the all-important factor in inflammation and the repair of injury (as also in the production of immunity), in order that, having put clearly forward the tenets of those upholding the theory, I may the more readily state wherein lies the strength and wherein the weakness of the doctrine.

The theory of phagocytosis as set forth in Metschnikoff's later writings may be summed up in the following theses: —

1. That certain of the leucocytes present in the blood and lymph, notably the finer granular oxyphile or neutrophile, and the large hyaline, are capable under certain conditions of taking up bacteria which have gained entry into the system.

2. That in addition to these the splenic corpuscles, the cells forming the endothelium of capillaries, and sundry other fixed cells of mesoblastic origin, possess the same property, although they exert it to a less extent.

3. That these phagocytes seize upon and destroy living and active microbes under certain conditions.

4. That the more virulent the microbe the less the tendency for the leucocytes above mentioned, and for the other fixed cells, to take up the bacteria. The less virulent the microbe the more extensive the phagocytosis.

5. That in addition to this power on the part of certain cells (the phagocytes) to take up and destroy certain bacteria, another factor has to be called in to explain why the wandering cells of the body migrate towards the focus or foci where the micro-organisms have gained an entry into the body. This factor is the "chemiotaxis" exerted by the products of bacterial growth, and by some other substances, such, for example, as the products of death of tissue and of wandering cells; and experimentally also certain chemical irritants as, for example, turpentine and mercury. In the case of the virulent microbes the leucocytes are not attracted to the focus of infection. There is a "negative" chemiotaxis, and thus, in the absence of phagocytosis, the proliferation of the microbes takes place without hindrance; whereas the less virulent microbes and their products attract the leucocytes, they exert a positive chemiotaxis, so that there is a migration of leucocytes through the capillary and venous walls to the focus of infection, and the leucocytes taking up the microbes tend to arrest the infective process.

6. That the leucocytes may become accustomed and eventually

attracted to substances from which at first they were repelled, and thus a negative may be transformed into a positive chemiotaxis.

7. That the cells, having once acquired positive chemiotactic properties in relation to the products of any specific microbe, retain and transmit these properties through a series of cell generations, the length of which varies according to the microbe, the extent of the primary reaction, and the idiosyncrasies of the individual.

8. That, consequently, the cure of zymotic or mycotic disease, whether localised or general, and immunity also, are mainly brought about by the activity of special cells (the phagocytes), and are primarily dependent upon the attraction existing between these cells and the products of bacterial metabolism.

9. The process of inflammation is essentially the endeavour on the part of the organism to promote the migration of leucocytes, and to aid the inclusion and destruction of the irritant. "The essential and primordial element of a typical inflammation is a reaction of phagocytes against the irritant (*agent nuisible*)." (14) Or, more fully, "inflammation is to be regarded, on the whole, as a phagocytic reaction of the organism against irritants, — a reaction which at times is accomplished by the wandering cells alone, at times with the aid of the vascular (fixed) phagocytes, or with that of the nervous system."

10. That in rare cases bacteria may be affected if not destroyed by extracellular action, by substances derived from the leucocytes and dissolved in the surrounding lymph.

In the terms of this theory, then, phagocytosis is the all-important factor in the inflammatory process, the vascular, exudative, nervous and other phenomena being auxiliary means whereby the phagocytic properties of the wandering and fixed mesodermal cells may be brought more fully into action: the determination of leucocytes that I have described is almost entirely to be attributed to an endeavour on the part of these cells to take up and destroy the irritant.

It is necessary now to ask to what extent this doctrine is to be accepted. Certainly phagocytosis is a factor in the inflammatory process — no antagonist of this doctrine nowadays is prepared to deny this — but does it occupy the all-important position arrogated to it by Metschnikoff? Metschnikoff himself admits that there are certain wandering cells — the coarsely granular oxyphiles — which never act as phagocytes. When powers so great are found to belong to one set of leucocytes, is it likely that another set, which is also especially attracted to the inflammatory focus, is absolutely devoid of either bactericidal or antitoxic function? Or, to approach the matter from another standpoint, let us take a case supplied recently by Gabritchewski from Metschnikoff's laboratory. If a guinea-pig be rendered refractory to the bacillus of diphtheria, and if the vulva be cauterised and infected by a virulent culture of this bacillus, there results a necrosis of the surface layers. On the free surface of the necrosed region lie the proliferating microbes; apposed to the under surface of the necrosed area is a large

collection of migrated leucocytes. In about three days the necrosed tissue sloughs off, and recovery and repair ensue. But in this process little phagocytosis is observable. The phagocytosis is evidently not commensurate with the extent of the inflammation; and if, as Metschnikoff urges, the leucocytes are the all-important factor, their powers of defence must here include something beyond the incorporation of the micro-organisms. The same additional something would seem to be wanted to explain the healing of abscesses.

A crucial test of the importance of phagocytosis has been devised by Baumgarten, and repeated, with like results, by Sanarelli. If microbes be placed in an animal which has normally the power of withstanding the growth of such microbes; and if, further, they be so placed (in bags of filter paper, celloidin, or pith) that the leucocytes cannot attack them, although the body fluids can easily bathe them, then, if Metschnikoff be right, the microbes ought to flourish unaffected. Baumgarten and Sanarelli found that this is not so, that the microbes are destroyed despite the absence of phagocytes; but Metschnikoff, repeating these experiments, obtained diametrically opposite results. Both Baumgarten and Sanarelli are capable observers although it is true that the former by the very violence of his attack upon Metschnikoff has materially weakened his position. It is, however, difficult to explain away their positive results, or to arrive at a conclusion other than that under certain conditions the microbes may be destroyed without being ingested.

The Humoral Theory. — The conception that there is some agency besides phagocytosis pure and simple has led bacteriologists, in the study of phenomena of inflammation and immunity, to engage in a very remarkable series of experiments. Although some of them have failed to establish a satisfactory theory of immunity, they have led to results of such high importance as the discovery of the serum treatment of diphtheria and tetanus. The majority of these researches, indeed, bear especially upon the production of immunity, and only secondarily upon the inflammatory process. It is unnecessary for me, therefore, to describe them in detail; it will suffice if I indicate the direction taken by the more important among them.

First in order of time may be mentioned Nuttall's observations. In an attempt to repeat Metschnikoff's researches upon the destruction of the anthrax bacillus, this observer noticed that if he placed a fine canula containing a fresh culture of attenuated anthrax bacilli in the tissue of a rabbit's ear, there resulted in sixteen hours a rich cellular exudation; but phagocytosis appeared not to reach its maximum for twenty-two hours, and even then half of the bacilli lay free and not taken up by cells; and he found, further, that the free bacilli showed involution and degeneration to the same extent as did the ingested. This led him to study the effect of blood serum, defibrinated blood and lymph upon the bacilli, and he discovered that these fluids had a remarkably rapid action, destroying great numbers within a very few hours. Moritz, Traube, Von Fodor and others, had previously recognised this rapid

destruction of micro-organisms in the living blood, but Nuttall's very full research appeared to show conclusively that the bacteria-destroying power resided largely in the serum, and that in inflammation the exuded fluid rather than the leucocytes brought about the destruction of the microbes.

These observations were confirmed and extended by Nissen, Behring, and Buchner, and a most valuable series of contributions (see article on the "General Pathology of Infection") have been made by Hankin, Buchner, Vaughan, Tizzoni and Cattani, Behring, and others, upon the nature and properties of the substances to be derived from the blood serum of animals either naturally immune to certain diseases, or rendered immune by one or other procedure. What is more, it has been recognised that two orders of substances are recognisable: one capable of destroying pathogenetic microbes, the other not destroying them, but rendering their products inert.

It would thus at first sight appear that in these discoveries there is a direct contradiction to the theory of phagocytosis. Yet upon further study this is found not to be the case.

As was shown by Nuttall, at the commencement of these studies, the blood serum removed from the body acts far more rapidly and energetically than do the blood plasma and lymph within the body. The disparity of action between the two is remarkable. Thus Lubarsch has shown that in order to kill a rabbit by anthrax, by injection into the circulating blood, at least 16,000 virulent bacilli of the disease must be introduced: a smaller number produces only a transient disturbance. That is to say, the whole circulating blood can only destroy less than 16,000 bacilli at a time. On the other hand, one cubic centimeter (15 minims) of rabbit's blood serum can in a few minutes kill an equal or even greater number.

The Cellulo-Humoral Theory. — If the serum and if the blood plasma contain bactericidal substances, these must in all likelihood be developed by certain cells, and thus at bottom the humoral theory must be cellular; and the very fact of the great increase in the bactericidal properties of the blood immediately on its withdrawal from the body, must suggest that in the changes which occur in the extravascular blood there is a liberation and solution of bactericidal substances. Now the first and foremost of these changes is the breaking down of the leucocytes as the blood begins to clot. It may therefore be that this breaking down of the leucocytes, with liberation of their contents, is capable of explaining the increased bactericidal action of defibrinated blood and blood serum.

That the leucocytes contain bactericidal substances was first demonstrated by Dr. Hankin, who obtained from the lymphatic glands and spleens of animals immune to anthrax (dogs and cats), a proteid of the nature of a globulin identical with Dr. Halliburton's cell globulin β, and having a bacteria-killing power similar to that possessed by blood serum. In later observations upon the rat he showed that there was a relationship

between the amount and activity of these "defensive proteids" and the power of resistance of the animal to the disease. Thus Hankin showed that in animals possessing the power of destroying bacilli, the organs containing the largest collections of leucocytes yielded notable quantities of a bacteria-destroying substance.

For the last few years I have steadily urged this view, and observation after observation is proving it to be correct. Recently Buchner has shown that if sterilised emulsions of the gluten of wheat be injected into the pleural cavity of a dog and rabbit, its presence leads to the pouring out of an aseptic exudation peculiarly rich in leucocytes, and this exudation is more bactericidal than is the blood and serum of the animal. Further, Victor C. Vaughan is led to the conclusion that the bactericidal action is associated with the leucocytes by his discovery that from blood serum a nuclein (or nucleinic acid) can be separated — a body, that is, which so far has been found exclusively in connection with nucleated cells. This nuclein is either itself bactericidal, or has a bactericidal substance in intimate association with it; and Vaughan's observations and conclusions have been substantiated by the later and independent researches of Kossel upon nucleinic acid.

Further confirmation of the correctness of these views — that the bactericidal action of the blood serum is due to the breaking down of the leucocytes — has been supplied from the laboratory of Denys at Louvain. Denys and Havel have shown that the blood and exudations of the dog, freed from leucocytes either by filtration or by centrifugal action, lose their bactericidal action, regaining it when the leucocytes are reintroduced. Van der Velde induced an exudation rich in leucocytes by injecting into the pleural cavities of rabbits sterilised cultures of the pyococci, and killing the animals at various periods. Centrifugalising the pleural fluid, he found that the older the exudation, and the richer it had been in wandering cells, the more powerful its bactericidal action, — this being out of all proportion to the bactericidal action of the blood serum removed at the same time and similarly centrifugalised.

But more convincing proof has been gained by a study of the leucocytes in action. Even in 1887 Ribbert, in his studies upon the fate of spores of various species of aspergillus and mucor inoculated into the anterior chamber of the rabbit's eye, had found that two stages of reaction were recognisable: at first the spores and developing hyphal filaments became surrounded by dense clusters of leucocytes, which remained in apposition to, but did not ingest the micro-organisms. Nevertheless they appeared to bring about a weakening and lowering of vitality on the part of the spores and filaments, so that after a time other cells could manifest their phagocytic activity and take them up. Ribbert, it is true, attributed the lowering of vitality to the walling in ("Wallbildung") by the leucocytes, and consequent lack of nutrition; but the fact remains that he demonstrated a preparatory extracellular action upon the micro-organisms by the leucocytes.

Altogether the fullest and most important studies upon this extra-

cellular action have been those of Kanthack and Hardy. In their first communication to the Royal Society these observers showed (and their experiment can be repeated without difficulty) that if a drop of frog's lymph be placed upon a coverslip, with the addition of a few anthrax bacilli, and this preparation be suspended in a moist chamber, an examination extending over four or five hours reveals the following succession of changes: —

1. The coarsely granular oxyphile cells are strongly attracted to the bacilli: they move towards them, and apply themselves to their surface; their protoplasm, ordinarily sluggish, exhibits quick streaming movements. Next the eosinophile granules are discharged, and the bacilli begin to show signs of degeneration. During this stage the hyaline cells, the phagocytes proper, remain quiescent, and are not even attracted towards the bacilli.

2. The hyaline cells proliferate and eventually approach the masses of oxyphile cells surrounding the bacilli; they fuse with these — forming a plasmodium around the chains — and for the next hour or two nothing can be clearly made out as to the action of individual cells.

3. The first stage in the dissolution of the mass is the separation and wandering away of the oxyphile cells; next, the hyaline phagocytes containing remnants of the bacilli within vacuoles slowly break apart.

4. A third set of cells, with basophile granules, is observed to approach during this last period; as to their functions Kanthack and Hardy are a little doubtful.

Here, then, we have clear evidence of division of labour among the wandering cells of the frog: the coarsely granular oxyphile cells act as unicellular glands discharging or excreting their granules, and these granules dissolving appear to exert a deleterious action upon the bacilli, in consequence of which the hyaline cells are now capable of ingesting them. I may add that occasionally the coarsely granular cells may be seen to act when not in immediate apposition to the microbes; the number of granules in a cell may diminish, and at the same time neighbouring bacilli manifest signs of partial dissolution.[1]

Continuing their research Kanthack and Hardy have demonstrated these distinctions in the function of the different forms of leucocytes throughout the vertebrata up to man. They have shown that in general the hyaline cells act as the phagocytes of the lymphatic and cœlomic system; the finely granular oxyphile (neutrophile and amphophile) as the phagocytes of the hæmal system; while the coarsely granular oxyphile (eosinophile) when present possess excretory functions.

If capillary chambers filled with bacilli or their products, or some irritant such as nitrate of silver or turpentine, were placed under the skin, or in the peritoneal cavity, and allowed to remain there for periods

[1] Mesnil, in a long and often suggestive work, which appeared while this article was in the press, contradicts these observations of Kanthack and Hardy. Apparently he never once attempted to repeat their procedure, never once attempted the simple methods necessary to confirm their results. His criticism must therefore be relatively valueless.

up to twenty-four hours, they were found to contain a multitude of cells, chiefly of the cœlomic type. If the irritant were situated in such a position as to appeal to the blood-vessels of a vascular membrane rather than to the cells of the connective tissue spaces, then the cells were those of the hæmal system. In both cases in the earliest stages there was usually found a preponderance of the coarsely granular oxyphile cells. Even in cutaneous blisters induced upon themselves, while the main mass of cells present in the serous exudation were the finely granular oxyphile of hæmal origin, the coarsely granular were always more abundant relatively to the others than in the blood. The rate of accumulation was found to vary according to the irritant. Thus, comparing the action of the virulent B. anthracis and the harmless B. ramosus upon rabbits and guinea-pigs, it was seen that if cultures of these two forms were placed within capillary tubes and introduced into the peritoneal cavity, with the former only the coarsely granular oxyphile found its way into the tubes (even after seven hours); whereas with the latter enormous numbers of the hyaline phagocytes had invaded the chambers within two and a half hours. In the former case also the total number of invading cells of all kinds was very much less than in the latter case; and there was clear evidence of the abundant disintegration and dissolution of many of the cells. This destruction of a certain number of cells occurred, whatever the nature of the microbe introduced into the system; and, as these observers point out, it must profoundly alter the chemical constitution of the plasma, and may therefore play an important part in the struggle with the bacilli. They observed phenomena of the same nature as those of the frog's lymph, when they placed anthrax bacilli in hanging drops of human blister fluid and examined the preparations upon the warm stage, noticing here also the rapid diminution of the granules of the eosinophile cells.

Finally, it must be added that Metschnikoff (while misunderstanding wholly the drift of these last-mentioned researches) has recently admitted that the wandering cells are capable of exerting an extracellular activity upon the bacteria. Certain observations of R. Pfeiffer had revealed that, under certain conditions, when guinea-pigs have been rendered highly refractory to the spirillum of cholera, these microbes when injected into the peritoneal cavity are rapidly modified, becoming swollen and spherical before any phagocytosis has time to come into play; and this alteration was explained by Pfeiffer as due to the fluid secreted by the peritoneal cells following upon the inoculation. Without detailing Metschnikoff's criticism of the value of these observations, it will suffice to say that, carefully repeating them, he discovered that five minutes after such injection the leucocytes in the peritoneal fluid — "polynuclear," mononuclear, and eosinophilous — were surrounded by a layer of spirilla, while the lymphocytes and red corpuscles were entirely free from any such surrounding. Here in the immediate neighbourhood of the wandering cells, the short, curved bacillary forms could be seen to have undergone the transformation into globules. Metschnikoff further recognised a clear

zone, evidently of exuded liquid, between the leucocytes and the spirilla. Whether this be a true secretion, or an accompaniment of the death of the cells, he is not at present prepared to say.

In this way Metschnikoff admits that, besides phagocytosis, an extracellular action of the wandering cells does occur; so that now the only point of paramount importance to be agreed upon is the extent to which the extracellular activity is manifested *intra vitam*. Metschnikoff at present holds that it plays a very secondary part compared with phagocytosis; others, like Buchner in Germany, Denys in Belgium, Kanthack and Hardy in England, hold that its part is of high importance. Personally, while holding that phagocytosis has been conclusively proved to be of singularly high importance, I cannot but see in this extracellular action of active and of disintegrating leucocytes an adjuvant to the former factor, and one which under certain conditions is even of greater value to the organism in its attempt to neutralise microbic and other irritants. Whether the fixed tissue cells of the body have similar "extracellular" action upon living irritants, or not, is a matter that has not yet been ascertained. There are indications that this may be so.

Summary. — Thus, to sum up the facts gathered together in this chapter, the chief results of recent researches into the functions of the wandering cells, as they affect our knowledge of the inflammatory process, would seem to be the following: —

1. That in the higher animals there are several forms of leucocytes.

2. That a distinction can be made out in the distribution of the various forms, some being characteristic of the blood, others of the connective tissue spaces and of the cœlom and cœlomic fluid in general.

3. That the forms of cells accumulating during the inflammatory process consequently vary according to the region of injury.

4. That a variation is to be made out also in the rate of accumulation of the different forms of cells: the coarsely granular oxyphile (eosinophilous), which in the main are pre-existent in the connective tissue spaces, being attracted sooner than the finely granular oxyphile (neutrophile hæmal) and the hyaline (cœlomic) respectively.

5. That a further distinction is to be made out in the mode of action of these cells: the coarsely granular oxyphile never act as phagocytes, but possess excretory properties; the hyaline and finely granular oxyphile are characteristically phagocytic.

6. That the accumulation of leucocytes is due in part to migration, in part to proliferation *in situ*.

7. That under certain conditions (what these are and what their relative importance have yet to be more fully worked out) the phagocytes are capable of directly incorporating pathogenetic bacteria. The main conditions would seem to be the possession by the bacteria of relatively weak irritant or pathogenetic properties, and by the organism of relatively strong powers of resistance.

8. That under other conditions (where, for example, the microbes are endowed with fuller irritant properties, or the constitutional resistance is

lower) phagocytosis may be preceded by an excretory process on the part of certain cells, notably the coarsely granular oxyphile, whereby apparently the vitality and irritant properties of the microbes undergo a diminution. Here again we are as yet ignorant of the exact value of all the factors leading to active intervention of these excretory cells.

9. That the bactericidal and antitoxic action of the blood serum and body fluids outside the body is due to the liberation into these fluids of bactericidal and antitoxic substances step by step with the disintegration of the leucocytes.

10. That clearly this liberation of bactericidal and antitoxic substances by excretion from living cells, and by disintegration, does not obtain to the same extent in the fluids within the living body; nevertheless it does occur, more especially as the result of irritation, and its occurrence is fitted to explain those cases in which the amount of phagocytosis observable is not co-extensive with the disappearance of the microbic irritants.

11. That where the bacteria are endowed with great virulence, there the wandering cells migrating to the region are both fewer in numbers, and, being killed, undergo dissolution to a very considerable extent. This dissolution may in itself, by the liberation of bactericidal substances into the inflammatory exudation, hinder the proliferation of the microbes to a greater or less extent. If, however, the dissolution be unaccompanied by a massing of active leucocytes peripherally around the region of irritation, then the microbic irritants may be carried away from the inflammatory focus, and induce generalised disease.

To complete this summary I will here add other conclusions deduced from a study of the later stages of inflammation and discussed in a later chapter ("Upon the part played by the fixed Cells in the Inflammatory Process"), viz.: —

12. In the later stages of inflammation the growing fibroblasts may often be seen to contain leucocytes in process of digestion. Presumably, therefore, a certain number subserve nutrition.

13. Others are, in certain cases, recognisable in the lymph-spaces outside the inflammatory focus, containing the debris of dead tissue. Emigration can therefore occur as well as immigration.

14. The process of development of wandering into fixed cells has been observed; but this is the exception, not the rule.

15. The contrary process of development of wandering cells from degenerating tissue (muscle fibres) has also been recorded by more than one observer.

Chapter 2. — The Inflammatory Exudation

Whenever injury to the tissues leads to vascular dilation there is an increased effusion of plasma from the blood. The extent of this effusion varies greatly; it varies with the tissue affected, the state of the organism, and the quality and nature of the irritant. Dense

tissue permits of little exudation, while loose vascular tissue, under the action of an irritant of no great intensity, may undergo great exudative swelling. There is, for instance, a peculiar liability in serous and cutaneous surfaces (or more truly in subserous and dermal layers), when inflamed, to manifest abundant exudation. Their vascularity and the slight external resistance would appear to explain this liability. There is not the same tendency to abundant exudation from mucous surfaces save where, as in the alveoli of the lungs, the epithelium is reduced to a single layer of delicate flattened cells; on the other hand there is a marked tendency towards serous infiltration and swelling of the submucosa. That some general state of the organism is a factor concerned is seen when virulent anthrax bacilli are inoculated subcutaneously into an ordinary rabbit and into one that has been rendered immune: in the former the exudation is of a serous nature, in the latter little fluid is exuded from the vessels. The effect of the quality of the irritant is observable upon comparison of the results of inoculation of various microbes. Some cause little exudation of fluid. These are in general of low pathogenic quality, but not always; certain virulent microbes (such as those of tetanus) lead, when inoculated, to relatively little effusion of fluid from the vessels. On the other hand, it may be stated definitely that where in a moderately dense tissue the injection of a pure culture of a micro-organism leads to well-marked exudation, the micro-organism is of high virulence.

Can any meaning be ascribed to this effusion? Is it an attempt at increased nutrition in the injured region? It has been suggested, in accordance with Virchow's theory of inflammation, that the injury, stimulating the surrounding fixed cells, leads to increased local metabolism; and that the exudation is a means of bringing to the region the increased nourishment demanded by the increased cellular activity. But inasmuch as exudation is most marked in those cases where there is most profound and rapid cell destruction, and again at the early stage of the inflammatory reaction, when evidences of growth and proliferation of the fixed cells of the region may be, and most often are, wholly wanting, this view can scarcely be upheld. Yet at a later period of the process, and again in chronic inflammation, the overgrowth of the connective tissue cells would appear to stand in close relationship to the over-nutrition caused by the continued dilation of the vessels and the pouring out of excessive lymph into the tissues. There is, apparently, a close relationship between the increased exudation and inflammatory hyperplasia.

That the exudation exerts a "flushing out" action is very evident in many cases. Thus the inflammation induced by plunging an animal's leg into hot water is accompanied by great increase in the amount of lymph obtainable from the efferent lymphatics of the part. It is shown also by the presence of streptococci in the lymph channels outside the area of acute inflammation in erysipelas, by the frequent implication of the nearest lymph glands in suppurative disturbances, and by the appearance

of lesions, due to the direct action of bacterial products, in organs far removed from the focus of bacterial proliferation in such diseases as diphtheria and tetanus, wherein, as a rule, the bacteria remain strictly localised. It is clear that the exudation into an inflamed area can accomplish a removal of irritant matters. It is clear also, from more than one of the examples given above, that a process which may be beneficial to the region of injury may be harmful to the system as a whole.

It is interesting to note that this effect of flushing, in part beneficial, in part harmful, has, if I may so express it, gained a certain amount of recognition on the part of the organism. Where the irritant can be conveyed to the exterior an abundant exudative inflammation generally occurs — an abundant flushing; where it can be conveyed into one of the body cavities the same holds good; but here a mechanism is often called into action whereby the exudate with its contained irritants is held within the serous cavity for days and weeks after all signs of active inflammation have subsided. The organism, that is to say, would seem to restrain its drainage to the general lymphatic system. Where the irritant is merely the product of tissue change the profuse exudate is rapidly conveyed away; where, on the other hand, the injury is of bacterial origin, the passage of lymph from the focus of inflammation, is, generally speaking, not nearly so free; it is of thicker consistency and drains away slowly. In short, as I have already indicated, where the microbe is not too virulent a cellular rather than a serous inflammation is produced; and in place of abundant flushing an increased antibacterial and antitoxic action of the exuded lymph comes into play.

But besides this "flushing out" effect the exudation subserves another purpose, namely, dilution of the irritant and reduction of its injurious properties, so that it acts with lessened force upon the tissues, and permits the wandering cells to be attracted to the region where they may exert their functions. Where a comparatively mild physical irritant leads to abundant exudation the flushing out action appears to be in the ascendant, where microbic irritants cause great local inflammatory œdema, judging from the less extensive lymph flow from the region, the diluent action must be regarded as the more important. I have already pointed out that a relation may be traced between the intensity of bacterial irritation and the extent of the exudation. In short, there may be great exudation under two apparently opposed conditions: in the presence of comparatively mild physical irritants, and in that of severe bacterial irritants. In the former case it more especially subserves removal, in the latter dilution of the poison.

The fundamental distinction between the inflammatory exudation and ordinary lymph is its richness in proteids. Whether we regard lymph as a filtrate pure and simple from the blood, or, with the majority of modern physiologists, follow Heidenhain in regarding it as the result of a selective filtration, it is eminently probable that in inflammation the exudate approaches in its composition more nearly to the blood plasma than does ordinary lymph. The dilatation of the capillaries, the conse-

quent thinning of the endothelial layer with, it may be, the opening of some lacunæ between the individual cells, and the direct action of the irritant upon these cells, may all be expected to aid the transudation. In this way the amount of proteid matter in the lymph may be increased. But equally important must be the addition of proteids due to the breaking down of leucocytes and tissue cells. I have already discussed this destruction of the cells, and need not here give the evidence of its occurrence.

In addition to the proteids the inflammatory lymph may contain other substances worthy of more than passing note. Of these the more important are ferments, the results of proteolysis (notably fibrin and its precursors, and peptones), and in many cases mucin, together with bactericidal substances, and, where bacteria are present, the products of their growth.

The presence and amount of these substances depend largely upon the intensity and character of the inflammation. Thus the total quantity of proteids, and the proportion of fibrin, albumin, and globulin present, vary within wide limits. The following table[1] of observations made by Dr. Halliburton shows well this variation in proteids, and the difference existing between inflammatory exudations and dropsical effusions: —

Pleural Fluid from	Sp. Gr.	Percentage Quantity of			
		Total Proteid.	Fibrin.	Serum-globulin.	Serum-albumin.
Acute pleurisy, Case 1	1023	5·123	0·016	3·002	2·114
,, ,, Case 2	1020	3·4371	0·0171	1·2406	1·1895
,, ,, Case 3	1020	5·2018	0·1088	1·76	3·330
Hydrothorax . . Average of three cases	1014	1·7748	0·0086	0·6137	1·1557

Between the amount of fibrin present in exudations and the amount of peptones there is an inverse ratio. Peptones are especially developed in connection with suppurative inflammation; and the more an inflammation tends to be suppurative the greater is the breaking down of the fibrin, as also of fixed and wandering cells, and the more evident the production of peptones, until in chronic abscess-formation of fair extent the peptones pass into the general circulation, and are excreted and recognisable in the urine.

Into the discussion of the mode of formation of fibrin I need not enter here, intimately connected as the subject is with the inflammatory process. The greater text-books of Physiology enter exhaustively into the matter. Suffice it to say that, as in the blood, a direct relationship

[1] These figures are thoroughly in accord with those of other analyses by Reuss, Hofmann, Mehu, and Letulle.

is made out between the breaking down of leucocytes and the development of this substance in inflammatory exudations.

It is in connection with inflammation affecting serous and epithelial surfaces[1] that fibrin is most clearly recognisable, forming, it may be, thick coatings of the badly-named "inflammatory lymph" over the inflamed surfaces. This deposit is in all respects comparable to the formation of thrombi in the blood-vessels. Here, as there, the deposit occurs only when the endothelium has undergone destruction and the roughened sub-endothelial tissues are exposed. And here also the fibrin may be deposited either in filamentous or homogeneous and hyaline form according to circumstances.

Leaving out of account coagulation-necrosis as not occurring in direct connection with exudates, it may be said that similar fibrin formation is frequently recognisable in connection with primary inflammation of parenchymatous tissues.[2]

The beneficial effects of fibrin formation in serous cavities have been rendered abundantly manifest by the increase in abdominal surgery. No one who has followed any considerable number of operations for appendicitis can have failed to remark how, in case after case, despite the intricacy of the abdominal coils and their mobility, the strongly irritant matter produced by gangrene of the appendix, or oozing through perforations in it, is restricted within a relatively small space by the surrounding fibrinous adhesions which form rapidly between the intestinal loops. By this means alone the peritonitis is restricted and "regional," instead of being generalised from the onset. Even when inflammation (as in pericarditis) affects the whole extent of a serous cavity, the layer of fibrin acts as a protective coat closing the lymphatic stomata, hindering the free absorption of the morbid material by the lymph and blood-vessels, and filtering bacteria out of such fluid as does find its way through to the tissues beneath. It is not a little remarkable to call to mind how case after case of purulent pericarditis or purulent pleurisy may be examined in which, despite the intense suppurative disturbance in the serous cavity, the tissues at the other side of the deposit of fibrin — the myocardium or the lung tissue — show little or no tendency to abscess formation. Let there be primary abscess formation or gangrene in the lung, and perforation of the pleura and hydrothorax may supervene; pleurisy, however intense, does not lead to this unless complicated by other disease. Let there be primary or metastatic abscess in the myocardium, then there may be aneurysm and rupture of the heart; yet such rupture produced by extension inwards of a purulent pericarditis is of the utmost rarity. Let there be inflammation originating in the submucosa of the intestines, as in enteric fever, and

[1] Of epithelial surfaces, more especially those covered by a single cell layer, as notably the pulmonary alveoli.

[2] Where there are abundant and distensible lymph channels there extensive clotting may be seen in the lymph. This is peculiarly well marked in the contagious pneumonia of cattle (contagious pleuro-pneumonia). In acute inflammation of various organs, by appropriate methods of staining, similar formations of threads of fibrin, often starting from cells as centres, may be observed in the tissue spaces.

perforation may result; general peritonitis, while often due to perforation, never — so far as I can call to mind — directly induces that event. In all these cases the natural protective layer of the serous surface is removed or gravely injured at a very early stage; and the layer of fibrin, replacing the serous endothelium, forms an effective barrier. I may add that the mucin, extruded so as to form a layer over inflamed mucous surfaces, presents a similar protective action.

Passing now to the ferments and ferment-like bodies present in the exudate, I may briefly state that these are not only generated and excreted by the pathogenetic bacteria present, but are liberated by the breaking down of the wandering cells. Abundant evidence of the existence of bacterial ferments capable of acting upon proteids, gelatine, sugars, etc., is supplied by the study of the growth of these microbes outside the body. That ferments also originate from the wandering cells has been demonstrated by Leber, who, placing pieces of copper in the anterior chamber of the eye, thereby produced a purulent collection devoid of microbes, and showed that the exudate was capable of digesting proteid matter.

It would seem, therefore, that, more especially in pyogenetic inflammation, the removal of dead tissue cells and dead leucocytes may, to a large extent, be due to the action of the inflammatory exudations, apart from any phagocytic action on the part of living active cells; although this also comes often into play.

Of the bactericidal substances present in the inflammatory exudate I have already treated. Here I need only repeat that the researches of Kanthack and Hardy, of Denys, and lastly of Pfeiffer and Metschnikoff, fully prove that substances capable either of destroying microbes or of hindering their growth are present therein.

Summary. — To sum up what is known concerning the inflammatory exudate, it may be said —

1. That the exudate varies in amount and in character with (*a*) the nature and intensity of the irritant, (*b*) the condition of the organism, (*c*) the region of irritation.

2. That while it undoubtedly augments the nutrition of the affected region, increased nutrition at the early stage of an acute inflammatory process would not seem to be of benefit or to play any important part. At a later stage and in chronic inflammation the increased nutrition in all probability aids the hyperplasia.

3. That in many cases the exudate exerts a beneficial action by flushing out the injured area.

4. That the exudate plays an important part in diluting the irritant.

5. That the development of fibrin in certain inflammatory exudates is associated with the breaking down of the wandering cells, and is of manifest benefit in so far as it circumscribes the inflamed area, and prevents the passage of morbid material outwards.

6. That the exudate may possess digestive functions, causing the pro-

duction of peptones; the ferments being developed from the cells alone when the exudate is aseptic, from these and the microbes together where pathogenetic microbes are present.

7. That the exudate may further contain substances, generated by the cells, capable of hindering bacterial growth, and of destroying pathogenetic microbes.

Chapter 3. — The Part played by Blood-Vessels

The study of the action and function of the leucocytes in inflammation has profoundly modified our conception of the inflammatory process. When the leucocytes were regarded as purely passive agents, and their diapedesis as purely secondary to modified conditions of the blood current and of the vascular walls, the theory of Cohnheim was that most generally accepted. And this theory regarded the changes in the vessels as of the first importance. Thus it was that for several years our attention was mainly concentrated upon the determination of the various changes of the vessel walls, and of the mechanism whereby these changes were brought about. Nowadays less attention is directed to this side of the inflammatory process, and it may be said that during the last ten years little advance has been made in determining the mechanism of the dilatation that accompanies inflammation.

The subject, indeed, is beset with difficulties. It is most difficult to observe the changes that occur in the cells forming the endothelium of the congested vessels; we are still, for instance, far from being sure whether the opinion of Arnold is correct, namely, that the leucocytes, and, it may be, a large portion of the exuded plasma, find their way out through the dilated stomata between the endothelial cells; or whether the leucocytes pass directly through these cells as one soap bubble may be passed through another. And when we come to discuss whether the inflammatory exudation be a filtration, or whether, on the other hand, it be more of the nature of an excretion, or what may be termed a selective filtration — certain components of the blood plasma being permitted to pass through, while others are withheld — we are met with the difficulty that, of the extravasated leucocytes, a varying proportion undergo rapid destruction and dissolution. Thus, in analysing the inflammatory serum, we are not dealing simply with the extravasated fluid, but with a fluid which in addition contains proteid and other constituents derived largely from broken-down white corpuscles, and in part, it may be, from the modified cells of the inflamed area.

Though Arnold's observations upon the altered condition of the vascular endothelium in inflammation appear at first very convincing, upon further study they seem at most to indicate that with dilation of the vessels there is an increase in the size of the spaces between the endothelial cells. They do not, however, prove that these are other than virtual spaces filled with intercellular substance; and indeed Arnold himself came eventually to the conclusion that some such substance was

present filling them. The fact that viscid, gelatinous substances injected into the circulation may be detected passing through these stigmata is not a proof that the spaces are actual; all it proves is that the walls are weaker in these regions: it must be remembered that increased force and increased intravascular pressure are necessary to promote the passage of the injected mass along the vessels. The passage of the mass through the walls may therefore be an "artefact."

There is this further difficulty in the assumption that these are actual spaces — that in acute inflammation the exuded fluid in general contains a smaller quantity of proteids than does the blood plasma. It is true, no doubt, that the stigmata are so small they may possibly act like the pores of a filter, and consequently may not permit the free passage of certain constituents of blood plasma. Yet, granting all this, if the same principles be in action as those governing the ordinary (non-inflammatory) transudation, we must, with Heidenhain, be inclined to regard the endothelium as playing not a passive, but an active role. To enter into the large subject of the nature of lymph would be to pass too far afield; recent researches, on the whole, favour the view that the inflammatory exudation is not a mere filtrate, but is the result of a selective activity on the part of the endothelial cells.

We have not a little evidence that these cells play an important part in the vascular phenomena of inflammation. To their power of taking up microbes and acting as phagocytes I have already referred; into their connection with the slowing of the blood stream I shall enter later. Here I would point out that microscopically these cells can be seen to alter during the inflammatory process; they become enlarged and project into the lumen of the smaller vessels, and in my experience this enlargement affects not only the cell bodies, but also the nuclei, which at the same time would seem to contain more chromatin and to stain more intensely. In cases of chronic inflammation the enlargement is followed by proliferation, notably in the arterioles and capillaries, — a process which may lead to the ultimate occlusion of these small vessels. And in acute inflammation, according to numerous observers, mitosis is to be seen occurring in these endothelial cells at an earlier period than in the surrounding tissues.

A further and very important process intimately connected with the proliferation of the endothelium of the capillaries is the formation of new vessels as the result of continued inflammation. It is true that Rindfleisch and others have described this as being brought about by vaso-formative cells situated externally to the vessels; and that others have advanced so far as to suggest that there are cells in the newly-forming granulation tissue which become hollowed out and gain attachment to the pre-existing capillaries in a manner wholly similar to that observable in the vascular zone of the chicken embryo. I have sought for such intracellular development, but never have I seen the slightest indication thereof; nor again have I been able to discover cells arranging themselves after the method described by Rindfleisch in

columns or parallel rows preparatory to the passage of blood between them and to the formation of a capillary.

The search for the earliest signs of new capillaries is a matter of peculiar difficulty. I will not peremptorily state that Rindfleisch mistook an arrangement of cells not unfrequently seen in granulation tissue for stages in the development of new vessels. I will only say that my own observations coincide with those of Arnold, and of the majority of those who have more recently studied the question, and lead me to regard the formation of new capillaries as originating from the endothelium of the vascular loops already in existence.

The first step in the process is often recognisable, in cases of pleurisy and pericarditis, in the projection of loops of pre-existing capillaries beyond the line which indicates where the serous endothelium used to be, and into the fibrinous clot now adherent to the sub-endothelial layer. Such loops are markedly distended, and "point," as it were, at right angles to the denuded surface. A similar pointing or giving way of the wall along the convex margin of the loop is also to be made out not unfrequently in newly-developed capillaries. In these there is not, as might be expected, a thinning of the endothelium along this outer margin, but certain of the cells on the contrary appear large and active. At times a small sharp protrusion of the vessel wall can be detected in the region of pointing. This is best seen in the capillaries that are themselves but newly formed, and composed of nothing but a layer of endothelial cells. In this layer the protrusion can be made out to be in direct continuity with the endothelial cells of the region. At first it is solid, but in the later stages it can be seen to be nucleated, and to be growing by proliferation of the endothelial cells which thus jut outwards. Even before any further change is noticeable in this projection from the capillary wall it may be seen to be united with a similar process originating from a neighbouring vascular loop. Finally, it would appear that the joined processes become hollowed out, and thus are developed into fully-formed capillary loops. It seems impossible to make precise observations on the phenomena of new vascular formation in its successive stages. I can but state that these appear to be the steps of the process. By what means the new vascular projections join together to form loops we are ignorant. Metschnikoff suggests that there must be an attraction between the neighbouring projections — a chemiotaxis — leading them to come into apposition; this, however, is no more than a suggestion. That they do join is very clear to those who have studied granulation tissue, or have observed the vascular network connecting the previously separated surfaces of a wound.

A further function of the vessel walls is to be seen in the slowing of the blood current. It is difficult, and in fact impossible, to explain this slowing by altered diameter of the arteries and veins. The alterations observed in the diameters of the vessels of the inflamed area are such as, acting alone, would led to increased rate of flow. Nor again is the apparent amount of exudation, and of lymph flow from the affected

part, sufficient to make it probable that (as Wharton Jones first suggested) the slowing is in the main due to the concentration of the blood, relative drying of the corpuscles, and consequent increase of friction: while this may be an adjuvant we must, I think, find some more potent factor. What this factor is was pointed out long ago by Lister, who, in 1858, noticed that coincident with the slowing of the blood stream, the corpuscles move sluggishly along the vessel wall as though attracted by it. Lister essayed to prove this by an experiment performed previously by Weber. He ligatured a frog's leg, then irritated a portion of the web by a little mustard, and found that, although the blood current had ceased, there was nevertheless an accumulation of corpuscles in the vessels of the irritated area, the corpuscles gliding into the affected region and becoming adherent there. Other observers have shown that this accumulation is not due to increased adhesiveness of the red corpuscles, inasmuch as similar slowing and stasis may be induced if the blood of the frog's leg be replaced by milk and the web irritated. In this case there is a gradual slowing of the stream of milk and accumulation of the fatty globules in the inflamed area. While in Lister's experiment the transudation of the plasma might explain the accumulation of the corpuscles, in this latter instance, as in ordinary inflammation, the observed transudation is insufficient to account for the accumulation and slowing. Although I cannot accept his experiment as conclusive, I am forced to concur with Lister to this extent, that in inflammation the endothelium of the vessel walls becomes altered, the cells becoming enlarged. With this, as evidenced by the conduct of the white corpuscles, they become more adhesive, and this adhesiveness with the associated increased friction between the vascular walls and contents I regard as the first factor in bringing about the slowing of the blood stream. Let the current once accelerated be rendered slower by this increased friction, then transudation may accentuate the accumulation of corpuscles.

Summary. — While there is very much yet to be learned concerning the part played by the blood-vessels in inflammation, and while our present knowledge of this branch of the subject can only be regarded as very imperfect, the following may, I think, safely be said to epitomise what is known at the present time: —

(1) That the vascular walls, and more especially the endothelial cells lining the capillaries, play an active and not a passive part in the inflamed area.

(2) These cells have the power of throwing out pseudopodia and of taking up non-motile bacteria.

(3) They are larger and more prominent during inflammation than they are under conditions of health.

(4) From them are developed the new vascular loops in cases of more chronic inflammation.

(5) They would seem to become more adhesive in inflammation, and by this, in the first place, to lead to the adhesion of the leucocytes and red corpuscles to their walls.

(6) Similarly they would seem to cause an increased resistance to the passage of the blood current, and in this way tend to slow the rate of blood flow.

(7) The slowing of the stream may further be aided by the passage through the walls of increased amounts of fluid from the blood.

(8) It is impossible by analysis of the inflammatory exudation to determine whether this be a mere filtrate or be the result of a selective activity of the endothelium. On the whole, taking into account the observations made upon ordinary lymph, the latter would appear the more probable.

Other properties of the blood-vessels in respect of inflammation will be better discussed in a later section in connection with the discussion of the part played by the nerves.

Chapter 4. — On the Passage of Corpuscles out of the Vessels

By his researches, Cohnheim (1867) forcibly attracted the attention of pathologists to the diapedesis of leucocytes in inflammation — a process which had already been described years before by Addison (1843) and Waller (1846) in England; and yet earlier (though without grasp of the connection between the diapedesis and inflammation) by Dutrochet, in France (1828). Cohnheim recognised the amœboid nature of the leucocytes, and saw that once outside the vessels they moved actively, but eventually he could not discover that their penetration of the vessel walls was anything but passive; and this failure on his part to recognise the true nature of diapedesis confirmed him yet more strongly in the view that the all-important factors in the inflammatory state were the changes in the vessel walls, and, it may truly be said, arrested his advance towards a fuller comprehension of the subject.

It must be acknowledged that there is much which would seem to support this view of the passivity of the leucocytes. No one is prepared to attribute active movements to the red corpuscles, nevertheless in inflammation a certain number of these escape through the vessel walls. In the inflammation affecting some organs, notably the lungs, the number effecting a passage is very considerable. If, then, the red corpuscles emerge passively, why should not the emergence of the white be passive also? Add to this the very important observations made by Cohnheim, that where the circulation is arrested by compression of the artery there diapedesis ceases. This, if invariably true, would seem to indicate that when once by changes in the vessel the leucocytes adhere to the wall, the further passage through that wall is due to the *vis a tergo* of the blood pressure.

This, however, is not a safe deduction to draw from the experiment referred to. When the artery of an inflamed area is compressed the stoppage of the blood stream not only reduces the pressure, but also affects the quality of the blood and the conditions of the vessel walls; moreover, it must profoundly affect the vitality and activity of the contained leucocytes.

These considerations alone render the experiment valueless as a proof of the passive nature of the diapedesis. Again the passage outwards of red corpuscles does not occur in the earliest stages of reaction to irritation; it never precedes the diapedesis of the leucocytes (save where there is gross injury), but follows it. A capillary or small vein in the inflamed frog's web, for example, may be seen wholly filled with corpuscles, the peripheral zone being quite annihilated, and numerous red corpuscles lying in immediate contact with the walls; nevertheless at first leucocytes only are seen to emigrate. This difference must be due to some special property of these cells. The leucocytes in the blood stream are not necessarily globular passive agents, but they are capable of independent movement. Leber, in his long series of studies, has pointed out that if, with due precautions, a hooked glass tube (closed at its outer end where it catches into the incision in the wall) be inserted into a large vein no thrombosis may be set up around the intravascular portion, and yet, upon removal, a large collection of leucocytes may be found in the tube, attracted by a drop of mercury placed within it, with normal salt solution. (Mercury is a substance which within the tissues leads to an accumulation of leucocytes.) Here, then, there must be active attraction and active movement of the leucocytes within the blood stream. And Lavdowsky has described very exactly what other observers had also noted, namely, that in inflammation the leucocytes in the outer zone of the blood stream do not simply adhere passively to the wall, but move backwards and forwards before they attach themselves and emigrate, as though seeking for a point of less resistance. At times this movement is in a direction opposite to that of the blood current.

If, then, both within and without the vessels, the leucocytes can be actively amœboid, it is strange that they should be passive in the process of diapedesis which to the eye has so characteristically amœboid an appearance.

As above stated, the compression of the artery passing to an inflamed area is in most cases sufficient to arrest diapedesis in that area, and I have suggested that this arrest may be due to the altered environment of the leucocytes. Now, if an embryonic form be taken, in which the tissues would seem to possess greater inherent vitality coupled with less sensibility, the arrest does not necessarily occur. Thus, Metschnikoff has noted that diapedesis of the leucocytes can be followed in the tadpole's tail after the animal has been curarised to such an extent that the heart has ceased to beat and the blood in the capillaries has been brought to a standstill.

It is evident, therefore, that with our present knowledge we must regard the diapedesis of the leucocytes as an active migration, and must look upon the blood pressure, the disposition of the blood stream, and the altered condition of the endothelium of the dilated vessels as adjuvants in the process. The slowing of the blood stream and the diminished pressure in the inflamed capillaries render it more easy for the leucocytes to accumulate close to the vessel wall; the dilation of the vessels and

consequent thinning of the walls, with the opening, perhaps, of larger spaces of cement substances or stigmata between the individual endothelial cells, render it more easy for the leucocytes to accomplish the passage; but the movement from within the capillaries to the tissue-spaces outside is an active process due to amœboid movement of the leucocytes themselves. The continuity of the vessel wall once destroyed, other cells — red corpuscles — may be pressed passively through the walls.

If this view be accepted, we are bound to look beyond Cohnheim's limit of changes in the vessel wall for the stimulus which, originating in the area of irritation, acts upon the vessel wall and the leucocytes in contact with it; and, having first set up changes in the former, so reacts upon the latter that they emigrate; or, to put it in other words, are attracted out of the capillaries towards the focus of irritation. It has already been shown that the movement of wandering cells in the tissue is due to the attraction of a diffusible product of bacterial growth and of tissue change, and of sundry organic and inorganic materials — a force to which the name of positive chemiotaxis has been given. This chemiotaxis must be invoked to explain the active emigration of the leucocytes from the capillaries, and again to explain its cessation under other conditions. Thus, while the exposed mesentery of a frog is a tissue in which diapedesis can be observed with facility under ordinary conditions, if it be washed with a weak solution of quinine the leucocytes in the vessels remain globular, cease to adhere to the walls, and do not emigrate. This fact, first noted by Binz, has been confirmed by several observers, among whom Disselhorst made out also that, if these same leucocytes be removed from the vessels, they exhibit their usual amœboid movements. The quinine has not paralysed them, as Binz supposed; but, as Metschnikoff pointed out, it has neutralised the previous positive attraction, a negative or repulsive chemiotaxis being brought into play. It is difficult to see how the above facts can be otherwise explained.

The view that diapedesis is an active process gains further support from, and at the same time explains certain interesting observations made by, Bouchard, Roger, and Ruffer. These observers have independently shown that in sundry instances the results of local injection of virulent cultures are greatly modified if, shortly before or coincidently, the microbes and their products are introduced into the circulation. Thus, as Ruffer points out, a drop of the culture of the bacillus pyocyaneus inoculated into the anterior chamber of the rabbit's eye leads ordinarily to a great migration of leucocytes — to an acute purulent inflammation. If, however, the toxins produced by this microbe have previously been injected into the circulating blood, no accumulation of leucocytes follows inoculation into the eye. Dr. Ruffer has also extended most suggestively certain observations of Roger. Subcutaneous or intramuscular inoculation of the rabbit with the bacillus of symptomatic anthrax leads to the production of a local abscess with extensive accumulation of leucocytes. After simultaneous injections of fluid containing virulent bacilli and their products into the vein of the ear and the muscles of the hind leg,

Ruffer found the rabbit dead, within fifteen hours, with a huge tumour in the inoculated limb. Here, upon examination, the muscle fibres were found widely separated by exudation fluid, in which there had been great multiplication of the bacilli; but leucocytes were entirely absent. In both of these cases we have therefore diapedesis and determination of leucocytes following the purely local action of the toxin; want of diapedesis and absence of leucocytes when the toxin at the same time circulates in the blood stream. If any large proportion of the leucocytes which find their way to a focus of irritation emerge from the blood stream, these divergent results are only to be explained by some theory which is capable of reconciling the difference in the action of the leucocytes when they are circulating in normal and toxin-containing blood respectively.

Now, the results in these two cases are entirely consonant with what we know concerning the sensitiveness and reaction to stimuli not only of unicellular organisms, but also of the higher animals. Organisms, whether lowly or of most complex development, only perceive and react to alteration in their environment when the alteration exceeds a definite ratio. Thus, as Pfeffer has pointed out, a motile bacterium (the "B. termo") is attracted towards solutions of peptone: if it be already in a peptone solution, in order for it to be attracted towards and move into a more concentrated solution, this last must be five times as strong as is the former. The only possible explanation that I can see of the above observations of Ruffer and Roger is that the passage and want of passage of the leucocytes out of the vessels depends upon the ratio of diffusible bacterial products present in the blood stream and in the tissues respectively. Where the products are localised at one focus in the tissues, the leucocytes are attracted out of the unaltered blood, and there is active diapedesis; where there was already a solution of the bacterial products in the blood, the ratio of difference between the percentage amount of toxin in blood and tissue may be insufficient to stimulate the leucocytes; no diapedesis then ensues.

As is well shown in the experiment with symptomatic anthrax, the presence of the bacillus and its products in the circulating blood did not prevent inflammation at the region of local injection; inflammation and exudation were abundantly manifest — there was, in fact, a more extensive exudation than ever. The irritant — that is to say, the toxic products of the bacilli — at the point of injection was in no wise hindered from exerting effects upon the fixed cells of the vessel walls, and promoting all the changes in calibre and condition of the walls and in the blood stream characteristic of inflammation. But with vascular changes, if anything more prominent than in the case where local inoculation alone had been practised, the leucocytes stayed within the vessels: now the only cause to which we can attribute this abstention of the cells from emigration, is lack of attraction — certainly not lack of vascular change or lack of blood pressure.

Summary. — I am thus led to the following conclusions regarding

the passage of cells out of the blood stream into an inflamed area : —

1. The diapedesis of the leucocytes is, as the name implies, an active and not a passive process; it is due to active amœboid movements on the part of the cells.

2. The stimulus leading to diapedesis is that of positive chemiotaxis. It is the attraction exerted upon the leucocytes by the diffusible substances associated with the irritant.

3. Irritants, if themselves diffusible, or the diffusive substances developed while the irritants are within the tissues, are capable of two separate actions: one direct upon the vessel walls, leading to vascular changes; the other through the walls upon the leucocytes, whereby emigration may be induced.

4. These two actions need not (and frequently do not) manifest themselves pari passu.

5. In relation to diapedesis, the dilation of the vessels, the altered rate of blood stream, the altered disposal of the corpuscles in the stream, and the modified endothelium, may all be regarded as adjuvants.

6. The passage of red blood corpuscles from the blood-vessels into the inflamed area is passive, due to the blood pressure and to lack of continuity of the vessel walls. Such lack of continuity is afforded in many instances by the migration of the leucocytes through the walls.

Chapter 5. — On the Part played by the Nervous System

If the vascular changes in inflammation were due to reflex influences proceeding from the central nervous system, and were in fact controlled by the centres in the brain and spinal cord (as has been held by the supporters of neuro-humoral theories) then, in the first place, there should be a rapid and almost immediate response on the part of the vessels of any region on the introduction of an irritant. But this is not by any means constantly to be observed. Thus, as Cohnheim pointed out, if croton oil be rubbed upon a rabbit's ear more than an hour may elapse before the first beginnings of hyperæmia can be detected; yet the inflammation eventually set up may be very intense. In the second place, section of all the nerves passing to any region of the body should have this effect, that injury in the region in question should, be unaccompanied by the ordinary vascular reaction. But this is not the case. Divide all the nerves which supply a rabbit's ear for example, and then injure that ear, either by heat, cold, or inoculation of pathogenetic micro-organisms, and inflammation manifests itself with all the stages recognisable in an ear with intact nerve-supply. The vascular changes which accompany inflammation can occur then independently of any central nervous influences.

We can proceed farther, and state that regions deprived of their nerve-supply are peculiarly prone to inflammatory changes. But this liability to inflammatory disturbances in such regions is not directly due

to the destruction of vaso-motor tracts and the cutting off of central influences from the vessels of the part, but is, it would seem, immediately connected with the loss of sensation. Divide the ocular branch of the fifth nerve of a rabbit, and, if the eye be not protected, ulceration and necrosis of the cornea manifest themselves in the course of a few days. Protect the eye, either by bringing the lids together or by placing a shade over it in such a way that dust and foreign particles are prevented from settling upon the surface, and no such ulcerative disturbance manifests itself. From this it is clear that the primary cause of the inflammation is not any trophic change in the region, but is the lack of sensation, whereby irritant substances are permitted to gain a lodgment upon the outer surface without any attempt being made to remove them. That, in addition, there is a lowered vitality in parts deprived of their nerve-supply, and that this renders those parts a more favourable seat for inflammatory disturbances is more than probable; nevertheless, this would not seem to be the primary cause of the increased liability to inflammation. [*Vide* art. on "Nutritional Retrogressive Changes."]

This, then, in the first place, is clearly recognisable—that the vascular changes accompanying inflammation can occur independently of central nervous influences. Hence it follows that there must be a peripheral nervous mechanism controlling the vessels. It remains, therefore, to determine the nature of this peripheral mechanism: is it wholly under the guidance of peripheral nerve cells situated in the vessel walls, or is it, in part at least, idiopathic? In the present state of our knowledge the answer to this question must be guarded. The more carefully the innervation of the various regions is studied, the more clearly is it demonstrated that throughout all the tissues of the body there exists a wonderfully fine and complicated network of nerve filaments with occasional isolated ganglion cells. Yet proof is wanting that this system in connection with the vessels is sensorimotor. Indeed, so far as regards the heart and ventricular muscle (which may be looked upon as the region of the vascular system wherein the motile portion of the walls has become specially developed), the researches of Romberg and His lead rather to the conclusion that the peripheral nervous system subserves sensation alone.

Dr. H. J. Berkley's careful series of researches recently brought together in a *Johns Hopkins Hospital Report* (Neurology II., 1894) throws much light upon the termination of the nerves in various organs, and upon the relation of these nerves to the vessel walls. Berkley finds in connection with the ventricular muscles a dense network of nerve filaments, with small bulbous terminations upon the individual fibres. These observations, it must be admitted, tend to weaken the belief in the idiomuscular, or, more truly, idioneural action of the heart muscle.

At the same time, the more the activity of the various tissues is studied, the more fully it is seen that many cells retain what may be termed reminiscences of an earlier and more embryonic condition in which their functions were varied and less specialised. There is an

inherent probability that the endothelial cells can react directly to stimuli, and that they are capable of idiopathic contraction and expansion on appropriate stimuli. We have seen that these cells are capable of taking up microbes, and thus seem to exhibit an independent activity similar to that observed in the amœba or the wandering phagocyte. If these cells, then, are capable of throwing out pseudopodia, and thus of enclosing non-motile bacteria, are they not capable of contracting and expanding, as a whole, according to the stimulus of altered environment? As a matter of fact, such contractility of the endothelial walls of the capillaries has been demonstrated by Klebs and Severini. I cannot but conclude, then, that the endothelium of the capillaries is to some extent self-regulative or neuro-muscular. It is quite possible — but "non-proven" — that the muscular coats of the smaller arteries are likewise capable of self-regulation, and respond directly to stimuli.

This view — that the vascular phenomena of inflammation can occur independently of the central nervous system and of the peripheral nerves — does not imply that the nervous system, central and peripheral, is without its influence upon the process; far from it. We have evidence, in the first place, that the state of the vascular walls is modified after destruction or severance of the nerves. I do not here refer only to the consequent alterations in calibre of the vessels, but also to the changes in other properties. Thus Gergens, and to a less extent Rütimeyer, noticed that after destruction of the spinal cord the blood-vessels of the frog permit a larger quantity of fluid, and even particles of granular colouring matter, to permeate them.

In the second place, we have evidence that the central nervous system exercises some direct influence upon the inflammatory process. From Cohnheim onwards it has been a matter of common observation that when all the nerves of a part have been severed, the stages of the process succeed each other with greater rapidity. It may be that the modified state of the capillary walls, noted in the preceding paragraph, is capable of accounting for this fact, and that, in the absence of central influences, dilation of the vessels and exudation of fluid lead to the cardinal symptoms of redness and swelling, with associated changes in the tissue, at an earlier period.

Of the part played by the different sets of nerves the external ear of the rabbit again furnishes an excellent study. This part has a double nerve-supply through the auriculars (major and minor) passing from the cervical plexus and the sympathetic branches proceeding from the superior cervical ganglion: stimulation of the former leads to dilation of the ear vessels, of the latter to contraction of the same. If, as shown by Samuel, the sympathetics be divided on the one side, and the auricular branches upon the other, the ear vessels of the former side become widely dilated, and those of the latter markedly constricted. Under these conditions, if both ears be subjected to the action of water warmed to 54° C., there is a characteristic difference in their reaction. In the organ deprived of sympathetic influence the

congestion and hyperæmia become yet more pronounced: an acute inflammation sets in which proceeds rapidly to recovery. In the opposite ear, with its constricted vessels, no hyperæmia is set up; but there is stasis, and gangrene may supervene. These results have been confirmed by Roger, who, taking a rabbit and dividing the sympathetic on one side and then inoculating both ears with like quantities of a culture of the streptococcus of erysipelas, found that the erysipelatous process manifested itself much more promptly upon the paralysed side, and came to an end at an earlier date. The reverse was the case when the auriculars of the one side had been divided: here the process was of slower development than on the intact side, and of slower course, resulting in mutilation of the organ.[1]

The inference to be drawn from these observations is that section of all the nerves passing to the rabbit's ear permits the inflammatory process to run a more rapid course; section of the sympathetics (vaso-constrictors) alone has the same effect; while the uncontrolled action of the sympathetics after section of the auriculars (vaso-dilators) hinders or prevents the manifestation of the ordinary processes of inflammation, and by preventing the destruction or removal of irritant matter favours necrosis of the tissues. We have yet to learn whether these results are capable of a general application, and to discover how far they are borne out by clinical observations on diverse cases of localised paralysis. So far as they go they afford direct evidence of the power of the central nervous system to modify the course of the inflammatory process, while they demonstrate admirably how potent an auxiliary is the dilation of the vessels in the inflammatory process.

Other evidence that the state of the nerve-supply of a region influences the manifestation of inflammation is afforded in sundry neuropathies. In all of these, in the present state of our knowledge, it is difficult to trace out the nervous factors associated with the lesions to which I refer. Our knowledge of the respective influences of trophic and vaso-motor nerves is far too limited to permit us to say more than that a relation exists between the condition of the nerve-supply of the affected area and the inflammatory lesions there observable; that in a certain number of cases inflammation affecting the area supplied by one branch of a nerve may have associated with it definite inflammatory disturbances in the areas supplied by other branches of the same nerve, and that, similarly, when inflammation affects a viscus, inflammatory phenomena may be sympathetically developed in regions innervated from the same area in the brain or spinal cord. I have already given examples in support of the first statement: the familiar redness, swelling, heat and pain of the side of the face which may accompany toothache is an example in support of the second, while the condition of labial herpes in pneumonia is an evidence of the results of

[1] Although these results have been criticised by Samuel and other observers, upon reviewing carefully the whole literature of the subject, I cannot but think that the above paragraph represents the general trend of more recent work.

the third. Another example is to be found in the acute nephritis, which at times rapidly follows the passage of a catheter, or the impaction of a stone in the urethra. It is not unlikely that many of these sympathetic inflammations are not direct, but secondary. Thus, the first noticeable symptom of catheter fever is suppression of the urine. Such suppression might be brought about either by reflex contraction of the renal arteries, or, contrariwise, by reflex great dilatation and congestion of the vessels of the kidneys. If it be caused by the former then the nephritis can only be regarded as secondary, and as due to the injury done to the organ by the stoppage of its blood-supply for some little time.

From the multitude of the factors involved, these examples, taken separately, afford at most only a great probability that the nervous system can directly originate inflammatory changes. There is, however, the clearest proof that the nervous system does possess this power, and this is afforded by the results of certain observations upon hypnotic effects. There are persons susceptible to hypnotic suggestion, in whom the suggestion that a red-hot substance has been placed upon the hand will, in the course of a few minutes, lead to great reddening of the part supposed to have been burned, and this reddening may be followed by great local exudation and swelling — in fact, by all the symptoms of acute inflammation. Here then actual inflammatory reaction follows supposed injury.

It is unnecessary to do more than point out the light that this intervention of the central nervous system throws upon the subject of counter-irritation, and upon the modifications of the course of inflammations brought about by idiosyncracy of the individual.

From what has been said in the preceding paragraphs, it follows that: —

1. Acute inflammation in all its stages may proceed regularly in the absence of all centrifugal nervous influences.

2. The vessels of an injured area are capable of reacting apart from central influences; it may be either directly, or under the control of a peripheral system of nerve cells.

3. The central nervous system is capable of modifying the process of inflammation. It would appear that when the vaso-dilators alone are called into action the successive stages of the process are accelerated. When the vaso-constrictors alone are acting the process is retarded.

4. Centrifugal impulses alone, apart from any local injury, may originate a succession of phenomena of inflammation in a part.

5. Hence, in all probability a nervous and central origin must be ascribed to some, at least, of the sympathetic inflammations seen to occur in areas supplied by the other branches of a nerve supplying a part primarily inflamed; and again in areas supplied from the same region of the brain or cord as the inflamed organ.

Chapter 6. — On the Part played by the Cells of the Tissues

As a consequence of irritation two opposed processes may be manifested in the cells of the affected area, — changes leading to impairment and death, and changes leading to overgrowth and proliferation; degeneration and regeneration.

Either of these two processes may, it is true, be wholly wanting. In very acute suppurative disturbances, destruction of the tissue cells and the steps leading to destruction may be the only recognisable changes. Again, in the first stage of most injuries, whether of mechanical, chemical or bacterial nature, degenerative changes are wont to take the lead. On the other hand, there are irritants so mild that little or no cell destruction results from their action; an extreme example of this category of inflammations is seen in those epithelial overgrowths commonly known as "corns," due, as Sir James Paget pointed out in his lectures, to intermittent pressure and irritation of moderate intensity.[1] Other examples are to be found in the "catarrhal" inflammations, in which there is marked initial overgrowth and proliferation of the cells of mucous membrane; and in tuberculosis, again, in which characteristically the earliest effects upon the pre-existing cells, produced by the presence and growth of the tubercle bacilli, are those of enlargement and multiplication — necrotic changes, as a rule, only appearing at a much later stage. Once more, in the later healing stages of injuries, cell proliferation may be in the field alone. Nevertheless, in a very great number, if not in the majority of inflammations, the two processes may be found occurring together — destruction and degeneration being in evidence at the focus of irritation, and growth and proliferation towards the boundary zone, where the irritant is acting in a less concentrated form.

Although the two processes are thus so frequently associated, it will be well, for the orderly review of our subject, to consider them separately.

Degeneration of the Tissue Cells. — Death of the pre-existing cells as an immediate consequence of injury cannot be regarded as one of the phenomena of the inflammatory process. Immediate death of the cells may be a result of injury, and the disintegration of the dead cells may in itself lead the way to all the symptoms of inflammation. But cessation

[1] It may very well be that this is not an extreme example. Neoplasms as a class, whether malignant or benign, not improbably develop as a consequence of some irritation having an intensity just sufficient to induce cell proliferation, and continued for a time sufficiently long to impress upon the cells of the affected tissues the habit of rapid multiplication. There is evidence both in animal and vegetable pathology favouring this relationship between inflammation and neoplastic growth.

The objection may be raised, with considerable force, that substances which lead to cell-proliferation are stimuli and not irritants, and that a line should be drawn between inflammation proper and overgrowth the result of irritation. I, for one, would willingly make this difference, but while it is easy to draw the line in certain well-marked examples, in others, as I shall proceed to show, cellular proliferation is so essential a part of the whole inflammatory process that the division becomes impossible.

of action is not reaction, nor is failure response, and throughout this article inflammation has been considered as the reaction following injury, and the response to it. Thus immediate death of tissue cells is resultant and not reactive, and may be eliminated from the category of the essential phenomena of inflammation.

The same is to some extent true of cell degeneration, but not entirely. While it is impossible nowadays to accept Virchow's old view, that inflammation is essentially a process characterised by increased nutritive changes in the cells of the tissues, it remains most probable that in very many cases irritation induces increased, even if perverted, activity of certain orders of cells. The proliferation, swelling, and more or less rapid degeneration of these cells cannot be wholly ascribed to the toxic influence of the irritant, but must in part be regarded as a result of over-stimulation and overwork. This is most noticeable in connection with catarrhal and parenchymatous inflammations. In parenchymatous nephritis, for example, such as that set up by cantharidin or septic infection, the cells especially affected are those whose functions are especially excretory; and their degeneration would appear to be intimately related to the performance of their functions. Such degeneration, preceded or accompanied, as it so frequently is, by excessive proliferation, may truly be regarded as reactive, and not as wholly and primarily destructive.

Of the degenerations which affect the tissue cells in inflammation (and often at the same time the leucocytes) there are many varieties; in fact, according to the nature of the irritant, one, or other, or all the degenerations affecting the tissues in different pathological conditions may manifest themselves, save, perhaps, simple atrophy and pigmental degeneration (as apart from pigmental infiltration). Most commonly recognised are cloudy and fatty changes, but mucoid and hydropic changes are far more frequent than is generally noted. Even so specialised a change as amyloid degeneration has been observed occurring locally in chronic inflammations — as, for example, in gummata; while in these same chronic lesions hyaline degeneration in the vessel walls is very often to be encountered.

There is also to be seen in inflammatory disturbances of moderately acute type a further form of degeneration, which receives a passing mention in the text-books, it is true, but so far has not to my knowledge been duly treated as an entity; nor has its significance been fully grasped. This is what may be termed "reversionary" degeneration. It is to be seen affecting tissues, in which the individual components in the fully-formed state are not single cells, but cell complexes or compounds. Such compounds are the voluntary muscle and medullated nerve fibres, and, as Grawitz has pointed out, the fat cells of connective tissue.[1] These are formed by the fusion and united growth of several cells;

[1] I here, and throughout this article, leave wholly out of account Grawitz's "slumbering cell" theory — a theory incapable of actual proof, and at variance with the cell theory upon which is based the entire superstructure of modern biology.

and in inflammation, as under other pathological conditions, the degeneration of the cell-compound as a whole manifests itself by a certain amount of proliferation of the nuclei (of the muscle fibre, sheaths of Schwann, and periphery of the fat cells respectively), protoplasm can be observed to accumulate around these active nuclei, and with the assumption by the component cells of an independent existence the degeneration may be said to be complete — that is to say, beyond this point only the shell and débris of the original compound are left to be considered.

All these degenerations are inevitably associated with disturbance of the functions of the affected cells, and lead to their death if the irritation which has induced them be continued. But death is not the final stage to be considered. The ultimate fate of the necrosed cells varies according to the situation of the inflamed area, the intensity of the irritation, and the specific character of the irritant. From a free surface the dead material may be freely cast off. In acute suppurative inflammations, whether superficial or deep, and, in general, wherever there is an abundant determination of leucocytes, there obtains a digestion and solution of the necrosed cells; and, as I have already pointed out, this is associated with the development of peptones and albumoses, and is brought about largely through the extracellular action of the leucocytes. When there is a large area of cell destruction, with well-developed encystment and limitation of necrosis by granulation tissue, there the solution of the dead material and subsequent absorption may be incomplete, and a fatty débris left behind, which may eventually become infiltrated with lime salts (the calcareous degeneration falsely so-called). In tuberculosis, despite the presence of many leucocytes in the immediate vicinity, the dead material of the centre of the tubercle undergoes very little absorption, but remains as an inspissated, cheesy mass. In syphilis, on the other hand, in large gummata, while there is similar death of the central cells and absence of removal, fatty metamorphosis does not occur nearly to the same extent.

Lastly, although very little is known about the subject, attention must be drawn to the fact that along with the tissue cells the intercellular matrix undergoes modifications or degenerative changes during inflammation. Among these, in all probability, is to be classed an increase in the amount of intercellular mucin, a mucoid degeneration. The inflammatory exudate is in many cases rich in mucin, and although our knowledge of the changes in the matrix is scanty, the fact that the tissue cells in general show little evidence of storage of mucoid or mucinogenous material, renders it probable that what mucin is formed is either excreted or elaborated between the cells. Connective tissue fibrils, which may be regarded as part of the matrix, undergo dissociation and swelling, and eventually, in acute inflammation, disappear. In chronic disturbances they are especially prone to hyaline change.

Regeneration of the Tissue Cells; Overgrowth and Proliferation. — In the lower animals, as we know, injury and actual removal even of a large portion of the body may be followed by the complete reproduction of

the lost part. In man, however, this reproduction of lost tissue is reduced to its lowest point; the higher the tissue the less, and the less perfect, the reproduction. Speaking generally, the tissues which show the greatest potentiality for reproduction are the least highly organised — those composed of similar units. The "connective tissue" — the lowest and most widely distributed — retains the largest powers of proliferation and hyperplasia.

In ordinary inflammation hypertrophy and hyperplasia of the connective tissue cells are absent at the focus of irritation. Here degeneration is predominant. It is in the peripheral zone, away from the maximum concentration of the irritant, that (as shown in case after case of Leber's long series of studies upon injury to the cornea), the connective tissue cells show signs of enlargement and proliferation, that they become more swollen and prominent, send out large processes, and may exhibit signs of active mitosis. It may be urged that this peripheral change is not inflammatory, but associated; yet, as I have already hinted, the signs of cellular regeneration may manifest themselves at so early a stage that it is impossible to disconnect them from the process of inflammation. This fact has been brought out with emphasis in Ranvier's interesting series of studies on irritation of the peritoneum by weak solutions of caustic substances. If a few drops of a 0·3 per cent solution of silver nitrate be injected into the abdominal cavity of a rabbit or guinea-pig an inflammation is set up which lasts for some days. At the end of twenty-four hours the portions of the serous coat of the abdominal contents which have been most affected are found denuded of their endothelium — the cells have died and disappeared; but in other regions, less strongly affected, the endothelial cells present the reverse condition of overgrowth: their nuclei are swollen; the protoplasm, instead of forming a flattened plate, is swollen, and presents stellate prolongations anastomosing with those of neighbouring cells. The underlying vessels at this period show abundant evidence of inflammation; they are congested, and leucocytes are being poured out into the mesenteric network. Within forty-eight hours there follows upon the inflammatory exudation a rich development of fine filaments of fibrin, and along sundry of these filaments the enlarged endothelial cells send processes. Some of the cells become enormous, 100 μ or more in diameter. In this extension of the cells along the fibrinous framework we have probably the commencing formation of organised adhesions. The endothelial cells at this stage have become so modified from their previous quiescent flattened state that even outside the body they exhibit amœboid movements.

Up to this time no signs of nuclear division manifest themselves. According to Toupet, working under Cornil, it is not until the fourth day that mitosis is recognisable in this form of inflammation. But while inflammatory congestion, exudation of fluid, and diapedesis of leucocytes is proceeding actively, the modified endothelial cells of the regions that have not undergone the severest injury are with equal activity engaged in what it is difficult to regard as other than a reparatory process.

As Baumgarten showed in his studies upon the development of tubercles, in the irritation set up by the growth of the B. tuberculosis in the tissue, a like overgrowth with proliferation of the fixed cells occurs in the immediate neighbourhood of the bacilli without any primary evidence of cell degeneration. It is true that of late the researches of Borel have thrown doubt upon Baumgarten's observations, but they confirm the earlier researches so far as regards the mitosis of pre-existing cells, and the absence of degeneration of these in the earlier stages of the tubercular growth. Borel would regard all the large epithelioid cells of the tubercle as modified leucocytes. For myself I cannot admit that he has proved this, careful as his researches seem to be; and until the leucocytic nature of these cells be firmly established I am inclined, with the majority of histologists, to regard many of them as similar in nature and origin to the modified cells just described in connection with simple inflammation.

The difficulty of determining the origin of the growing cells in inflammation has formed the greatest trial of the pathologist throughout an entire generation, and yet longer; nor can we now assert without chance of dispute what cells are mainly concerned in the formation of new tissue.

When we examine newly-formed granulation tissue we can distinguish cells of more than one type — (1) small round cells with polylobular and fragmented nuclei, (2) other cells containing oxyphil granules, (3) larger cells with a single nucleus and a relatively large quantity of protoplasm, and again (4) cells of varying but generally large size, varying in shape, but on the whole having the appearance of spindle cells with single oval nucleus and abundant protoplasm. These can be made out easily.

The first two forms of cells are clearly leucocytes. Further study of their fate shows that they disappear; they play no further part in the organisation of the tissue save that, as is well shown by Scheltema and Nikiforoff, many of them are absorbed by the growing connective tissue cells, and thus would seem to aid in their nutrition. The last form likewise presents, as such, no difficulties. These are fibroblasts — cells in the process of growth into connective tissue. But what is their relationship to the previous form, — to the round mononucleated cells with fairly abundant protoplasm, — what are these last, and what in short is the origin of the fibroblasts, — is it from leucocytes or from pre-existing connective tissue cells? Upon this most difficult question more ingenuity and more research have been expended than upon any other part of this well-worked field of inflammation.

There can be no doubt nowadays that a large proportion of the fibroblasts in granulation tissue are developed from pre-existing connective tissue cells. The general consensus of recent researches leads decidedly in this direction; and it is from the laboratory of Ziegler, who by his classical observations led pathologists for some years to hold the contrary view, that the studies have emanated which most conclusively show the part played by the connective tissue; the researches of Krafft,

Podwyssozki, Cœn, Fischer, and Nikiforoff, confirmed and strengthened by the researches of Arnold, Marchand, Reinke, and Sherrington, all bring forward evidence in one direction. It is the clearly recognisable pre-existing cells of the tissue — connective, endothelial and epithelial — which show most constantly the signs of nuclear division: every stage of enlargement, mitosis and cell division, can be made out in them. Even if we did not possess the information afforded by nuclear changes, the fact that new tissue is always developed in the immediate neighbourhood of pre-existing tissue would in itself point strongly to this same conclusion.

We may rest assured of this much. But can we advance farther, and state that all newly-formed connective tissue cells originate from the pre-existing cells of the tissue, and that none of them are derived from wandering cells? In the present state of our knowledge the answer to this question must be an unhesitating "No." If we base our observations upon the morphology of the cells in granulation tissue, we find that with our present methods the large, round, mononuclear cells seen therein are undistinguishable on the one hand from large hyaline leucocytes, on the other from one stage in the development of fibroblasts. If we examine into their properties we find that they act as phagocytes incorporating the multinuclear leucocytes. The fibroblasts, according to Nikiforoff's careful studies, have an identical action; so also, according to Metschnikoff, Ruffer, Borel, and others, have the large mononuclear hyaline leucocytes. If we study their mode of division they, like the connective tissue cells, exhibit indirect or nuclear division. It may be (as has been more than once suggested) that the large mononuclear hyaline leucocytes differ from the other forms in being of endothelial origin. Were this so a path would be found out of our present difficulty. Certainly the most that can now be said is that it is quite possible that among the higher animals this one form of wandering cell may be contributory to new fibrous tissue formation, quite possible that the connective tissue cells which develop as a result of inflammation are not all derived from the pre-existing cells of the region.[1]

It must be borne in mind that leucocytes, endothelial, and connective tissue cells are very simple forms of tissue, that they are all of like mesoblastic origin, and thus being homogeneous, may be more variously modified, without impairment of activity, than more highly specialised cells. I must here add that in lower forms — in the tadpole's tail, for example — Metschnikoff has followed day by day the transition from leucocyte into typical connective tissue cell, and that, largely in consequence of these observations, French pathologists hold the view that the leucocytes enter far more actively into new tissue formation than I here recognise. The German school, with the exception of Arnold (whose

[1] In this connection may be mentioned the observations of Metschnikoff, confirmed by Barfurth, and more recently by Dr. Joseph Griffiths, which show that in the degeneration and disintegration of muscle fibres (of the tadpole's tail) the proliferated nuclei of the fibres become the nuclei of individual wandering cells — leucocytes.

views correspond on the whole with my own), has with Ziegler passed over to the opposite camp of connective tissue only from connective tissue. For myself I have carefully sifted the evidence adduced by either side. What is said above gives, I believe, the estimate of the matter for the time being; while what follows gives in brief the state of our knowledge of the part played in inflammation by the tissue cells in general.

(1) Two series of changes may occur in the cells of an inflamed tissue, which may be included under the terms degeneration and regeneration respectively.

(2) The extent to which one or other of these series of changes predominates varies with the nature and intensity of the irritant.

(3) Degeneration and death of the tissue cells may be a direct and immediate result of the presence of the irritant, and then can scarcely be regarded as essential phenomena of inflammation. Or they may be of more gradual onset, associated with evidence of over-stimulation and increased activity of the cells.

(4) Fatty, cloudy, hydropic and mucoid are the most frequent forms of degeneration affecting the tissue cells in acute inflammation; hyaline in chronic; other forms are rare.

(5) The ultimate fate of the necrosed cells varies as the situation, intensity of irritant, and specific character of irritant.

(6) Cell-proliferation is so constant an accompaniment of certain forms of inflammation that it is impossible to regard this as an adjunct and not as an essential part of the process.

(7) The tissues which show the greatest potentiality for reproduction in consequence of inflammation are those which are least highly organised.

(8) The origin of fibroblasts and new connective tissue cells cannot be regarded as entirely determined, but this much would seem to be clearly demonstrated: (α) That a large proportion of the fibroblasts are derived from pre-existing connective tissue cells. (β) That in lower forms — as, for example, the tadpole — leucocytes can be seen to develop into connective tissue cells. (γ) It is quite possible, indeed probable, that in the higher animals one form of wandering cell, the large hyaline mononuclear, contributes to the formation of new fibrous tissue.

Chapter 7. — On Fibrous Hyperplasia and its Relationship to Inflammation

The succession of changes from embryonic cells to fully-formed tissue can best be studied in cases where there has been a relatively large area of destruction — as, for example, after severe burns, or excision of organs or large portions of organs; or again, where inflammation has been of a chronic character.

If healthy granulation tissue be examined, the process of growth is seen to originate in the immediate neighbourhood of if not in direct

connection with the dilated new capillaries. It is around these vessels, formed of little more than a single layer of cells, that the fusiform fibroblasts are in greatest abundance. At a later stage, in regions more remote from the advancing margin of the granulations, the fibroblasts have a more general distribution in the intercapillary spaces, and are more elongated; around them may be seen the earliest wavy fibres of white connective tissue. These are essentially of cellular origin — as much so as is the substance of striated muscle fibres. The elongated fibroblasts not only break or extend at their poles into fine processes, but also along their sides the protoplasm undergoes modification into fine parallel fibrillæ. With the continuance of this change the cells become smaller and smaller until little is left but the attenuated nuclei, often so flattened and narrow as to be scarcely recognisable. It is generally accepted that the fibrillar substance contracts with increasing age; certainly the newly-formed cicatricial tissue diminishes greatly in volume, and with this diminution the previous great vascularity of the part disappears; the capillaries shrink until the majority become completely occluded. Thus in place of the abundant, soft and succulent granulation tissue, rich in cells, blood-vessels and exuded fluid, there is eventually a firm, shrunken, anæmic mass of fibrous tissue, with rare flattened nuclei, rich only in closely-pressed bundles of white, semi-transparent fibrils.

Fibrous hyperplasia is to be encountered in almost every tissue of the body as a sequence of very diverse morbid conditions. To speak of it in any case as "fibroid degeneration" is a misnomer. The overgrowth of any tissue, however lowly, is not a degeneration. Fibrous tissue may and often does become the seat of degenerative processes, notably the hyaline; but that is another matter. To regard every condition of generalised or localised fibroid change of the organs of the body as a chronic "—itis" is equally erroneous, until we have proof absolute that connective tissue only undergoes excessive growth directly or indirectly under the stimulus of injury. It is interesting to note the opposed tendencies of the two branches of our profession on this subject; the surgeons strive to restrict the idea of inflammation to acute pyogenic disturbance, the physicians to extend the idea so as to include all cases of chronic progressive "fibrosis." I will not say that the latter is as untenable a position as the former, for it is a matter of peculiar difficulty and delicacy to state what is and what is not an inflammatory fibrosis; after all, there is more danger of being tossed about helplessly in the Charybdis of including too little, than there is of striking upon the Scylla of including too much in our idea of inflammation.

Here I wish to point out how divergent are the conditions which lead to fibroid hyperplasia, and to draw attention to the fact that there is reasonable ground for not classing all forms under the one common heading, even though the resulting appearances may be undistinguishable and the effects the same.

Cicatricial fibrosis presents little difficulty; it is plainly the result of

inflammation; so too is the fibrous overgrowth upon chronically inflamed serous surfaces. Capsular fibrosis is clearly of the same nature; it is to be seen around foreign bodies, around chronic abscesses, in the walls of tubercular cavities, and encapsulating tubercles, gummata, and other neoplasms inflammatory and non-inflammatory. Allied to these is the fibroid replacement in old infarcts (including that following upon "myomalacia" cordis). Here, studying a series of cases, it can be made out that the necrosed material becomes surrounded by a zone of inflammation, and that, with the passage of leucocytes into the dead area and absorption of the effete material, there is soon manifest a new connective tissue overgrowth advancing inwards from the periphery.

Among the generalised scleroses there is one form frequently encountered which may, without hesitation, be regarded as the accompaniment of inflammation. This is seen well in the general interstitial nephritis accompanying subacute and chronic parenchymatous inflammation of the kidney. Of similar nature are some forms at least of hepatic cirrhosis, diffuse syphilitic cirrhosis, the diffuse tubercular cirrhosis to which attention has more especially been drawn by French pathologists, and an extensive pericellular cirrhosis in cattle, which I have of late been engaged in studying, due, it would seem, to the abundant multiplication of a diplobacillus in the bile capillaries and liver substance. Whatever be the immediate cause of other forms of cirrhosis, overgrowths of fibrous tissue would appear in these to precede atrophy of the liver cells, and to be associated with the presence of an irritant.

But there are other varieties of fibroid growth concerning which it is less easy to arrive at a just conclusion. First may be mentioned the replacement or compensatory fibroses. An excellent example of this is to be seen in the sclerosis of well-defined tracts of the spinal cord following destruction of the ganglion cells governing those tracts, or sections of the fibres, at a point proximal to their trophic cells.

The fibrosis in these cases is not secondary to a progressive inflammation, but to a simple atrophy of the nerve fibres. These shrink, and their place is taken by fibrous tissue. Another equally instructive example is to be found in the dystrophic sclerosis of the cardiac muscle fibres to which attention has been called, more especially by Drs. Martin and Huchard. This occurs in certain cases of arteriosclerosis, and is best seen in the papillary muscles, the fibroid change occurring, not around the thickened arterioles, but at the periphery of the area supplied by each. The muscle fibres around the arterioles are healthy; but farther away, through lack of nutrition, they have atrophied, and their place is taken by a zone of fibrous tissue which frequently manifests hyaline degeneration. In this instance the morbid condition of the arteries is in itself a hindrance to active dilatation of the vessels, and the exhibition of the ordinary accompaniments of inflammation. Indeed this peripheral zone is singularly free from leucocytes, yet well-marked sclerosis appears nevertheless.

Can these be regarded as cases of inflammatory fibrous hyperplasia? According to our definition they may: the fibrosis ensues as a reaction to injury. It is legitimate to conceive that the dying and atrophic tissue elements here, as in the grosser condition of infarct, act as irritants. But, on the other hand, the only recognisable evidence of inflammation is this very extension of cicatricial tissue; and even this is strictly limited in amount, being just sufficient to replace the dead tissue, and nothing more.

Active hyperæmia is not a prominent characteristic of any stage in the first instance cited above, and is throughout absent in the second. Still, as I showed in an earlier portion of this article when treating of injuries to non-vascular areas, active hyperæmia is not absolutely indispensable.

Active hyperæmia is entirely wanting in yet another form of fibrosis — that resulting from passive congestion, whether of the blood (as in clubbed fingers, in that variety of cirrhosis of the liver which may result from obstructive lung or heart disease, and in the spleen of portal obstruction), or of the lymph (as in chronic œdema, sclerema, elephantiasis and macroglossia). Is this to be regarded as an inflammatory fibrosis? Everything points to the conclusion that connective tissue cells and their progenitors, like the Chinaman and the Polish Jew, can thrive and multiply upon a pabulum which is starvation to those of a higher standard. In passive congestion, as in obstruction to the onward flow of lymph, there results undoubtedly a bathing of the tissues with increased lymph. Can this alone account for the hyperplasia, or must we invoke the aid of the irritation or stimulus of retained effete matters contained in the lymph? This question is one that is most difficult to answer. Underlying it are the further questions whether one broad explanation can be found to apply to all cases of tissue hyperplasia; and whether cell growth in general, under physiological as under pathological conditions, is due to increased nutrition, or to stimulation of the cells, to increased physiological activity of the same, or to removal of pressure and other conditions preventing growth, or to a combination of all, or nearly all of these. This last question at present remains unanswered. In the examples before us of hyperplasia following passive congestion, one possible factor, that of removal of pressure from the cells, is absent; and we are narrowed down, I think, to two of the possible factors named above — relatively increased nutrition, and stimulation by effete matters. If it were shown that there are states in which stimulation or irritation by effete matters plays no part in the overgrowth of new connective tissue, then we could, I think, safely declare that forms of fibrous hyperplasia exist which cannot come under the heading of inflammatory fibrosis, and that the fibrosis of passive congestion may be included among them.

Now such conditions do exist. That increased nutrition alone can lead to hypertrophy of the tissues was established long ago by Hunter's classical experiment of transplanting the cock's spur on to the cock's comb, —

moving it from a slightly vascular to a richly vascular region. In the ensuing overgrowth there can here be no question of irritation by anything beyond the normal blood.[1] And passing from the general to the particular, we have evidence that there is such a condition as fibrous hyperplasia due, as it would seem, to increased nutrition unassociated with the presence of toxins or other cellular irritants. In his wonderfully painstaking series of observations upon arterial changes, Thomas has adduced two cases which he describes, no doubt, as examples of endarteritis, but in which the inflammation is not apparent, nor indeed any factor other than altered tension of the arterial walls leading to altered conditions of nutrition. He shows that immediately after birth there is developed a thickening of the intima —a connective tissue proliferation immediately below the endothelium —of that portion of the aorta lying between the ductus Botalli and the passing off of the umbilical arteries. During later fœtal life the umbilical arteries are the largest branches of the aorta; and, when the circulation through them is arrested, the aorta above is too large for the amount of blood requisite for the abdominal viscera and the lower extremities. The arterial current becomes therefore relatively slowed, and presumably, judging by the analogy of what occurs in the adult when large branches of the aorta are ligatured, the aortic blood pressure is for a time raised. With this slowing and increased pressure there appears a compensatory overgrowth of the intima leading to contraction of the vessel and its lumen. Generally speaking, when the area of distribution of an artery is diminished, as, for example, when a limb is amputated, the artery shows a similar proliferation of the intima. In both cases the blood remains healthy, and the intima has undergone no injury; the only recognisable change has been a slowing of the blood stream, and probably increased blood pressure; and as the intima is nourished, not through the vasa vasorum, but directly from the main arterial fluid, it would appear that with the slowing an increased nutrition is brought into action. I can see no satisfactory reason for calling either of these cases an endarteritis. It is quite possible that other cases of thickening of the intima are due not to irritation, but to increased nutrition brought about by heightened arterial tension. The difficulty urged by Councilman that high arterial pressure does not invariably lead to overgrowth of the intima is not, in my opinion, insuperable. It must suffice if here I point out that it is more than probable that certain cases of endarteritis are in no sense of inflammatory origin, or secondary to degenerative changes; but are primarily associated with nutritional changes. In this connection it was shown by Prof. Roy and myself that when the aorta of the dog is suddenly and greatly constricted, and as a consequence the pressure in the

[1] I here leave out of account a factor which may be important, but about which we know practically nothing—namely, the effect of altered innervation. I am forced to assume, perhaps wrongfully, that, as this factor plays a like part in all the cases under consideration, it may for present purposes be disregarded.

proximal portion of the vessel greatly increased, the plasma of the blood is forced into the cusps of the aortic valves, and vesicles of lymph make their appearance on the under surface in that region where fibroid thickening is most frequent in cases of chronic high arterial pressure.

Thus, to express briefly the distinction that I would draw between inflammatory and non-inflammatory fibrous hyperplasia, I would say that where *local injury* leads to increased nutrition of the connective tissue, with increased functional activity of the cells, the ensuing fibrous hyperplasia is to be regarded as of inflammatory origin; where, on the other hand, local injury is not recognisable as the primary cause of the cell growth, the hyperplasia must be held to be non-inflammatory. In passive congestion, obstructed lymph-flow, and increased nutrition consequent upon arterial change, as in the cases cited above, we can so far see no cause for the fibrous hyperplasia beyond altered conditions of nutrition; there has been no primary lesion in the affected regions inducing the reaction. Such cases must be considered as non-inflammatory.

But while I lay down this distinction, I must impress upon the reader that the last word has by no means been said upon this matter, and that further research may cause a radical reconstruction of our opinions.

Forms of Fibrous Hyperplasia

A. *Of Inflammatory Origin.*

Localised
1. Cicatricial.
2. Perivisceral.
3. Capsular.
4. Replacement—
   Gross (of infarcts, etc.).
   Fine (dystrophic sclerosis, etc.).

Generalised
5. Cirrhotic, associated with parenchymatous inflammation, interstitial and lymphangitic.

B. *Of Non-Inflammatory Origin.*

1. Hyperplasia of increased (arterial) nutrition.
2. " of venous congestion.
3. " of lymphatic obstruction.

C. *Neoplastic.*

1. Fibromata.

Upon the Increased Temperature of Inflamed Areas

Very little has of late been added to our knowledge in this division of our subject: what is to be said appears now to be so well established that I need do little more than state the main conclusions. The long controversy that raged before these conclusions were fully accepted, and

John Hunter's original views shown to be in the main correct, scarcely comes within the scope of this article.

1. The temperature of superficial regions is raised, it may be several degrees above the normal, by the onset of inflammatory hyperæmia.

2. The temperature of internal organs when inflamed may be raised above the normal, but undergoes no material increase beyond that of other unaffected internal organs tested at the same time.

3. The rise above the normal, which is often present, is an indication of the febrile state accompanying the inflammation, and not of locally increased heat production.

4. The increased temperature of superficial areas when inflamed is due, not to the production of heat in the part, but to the increased quantity of blood passing through it. When the congestion is so great that stasis ensues there may be actual decrease in the temperature of the part.

5. The maintenance of high external temperature may exert a favourable effect upon the duration and progress of specific inflammation. Thus Filehne has recently shown that the course of experimental erysipelas in rabbits is more rapid and more benign when they are kept at a high temperature than at a low. We possess no clear evidence that this is due to the unfavourable effect of the heightened temperature on the growth of the microbes. Pasteur's well-known experiments upon the production of anthrax in fowls (ordinarily insusceptible to this disease) by lowering their temperature can be explained on other grounds. We have abundant evidence that heightened temperature promotes vascular dilation: the experiment of Filehne may therefore supply a further demonstration of the favourable effects of dilation of the vessels and hyperæmia in the inflammatory process.

6. Low external temperature, or the application of cold to the surface, contracts the vessels: hence, upon the lines of what has already been said, it would appear that

(*a*) It is calculated to diminish the amount of exudation.

(*b*) It is calculated in consequence to diminish the pain associated with inflammation.

(*c*) It has no directly good effect upon inflammation due to the presence and growth of pathogenetic micro-organisms, but may have the reverse effect of preventing the fullest reaction on the part of the organism.

(*d*) Where the irritant does not itself grow and multiply, or present cumulative action, there the application of cold may not only be of no harm, but of positive advantage, by lessening the inflammatory reaction and preventing this, where extensive, from being itself a cause of further injury to surrounding tissues.

The increase of systemic heat will be considered in the article on Fever.

PART III. — On the Various Forms of Inflammation

Chapter 1. — Classification

The minute changes which characterise the process as it affects one or other organ, and the various specific forms of inflammation, will be fully described in special articles. I have only to indicate more general causes and main varieties. To give a complete classification is impossible unless each separate tissue be taken in order, for each tissue presents peculiarities either in liability to inflammation, or in the course assumed by the process. Even to attempt a classification in broad outline is beset with difficulties, for the inflammatory manifestation varies, not according to one or two series of causes, but according to four at least; the permutations are thus so numerous, and the appearances so varied, that to give an adequate scheme of classification would require a diagram in four dimensions. These four causes of variation are —

A. Nature of tissue affected. B. Position of tissue affected. C. Intensity of irritation, or more correctly ratio between resistant powers of the organism and intensity of the irritant. D. Nature of irritant.

A. Nature of Tissue affected. — As I have already shown in the first portion of this article, there is in the earlier stages of the process a difference in the reaction of vascular and non-vascular tissues, the one series exhibiting marked congestion and vascular disturbance, the other not. At a later stage, or in more chronic irritation, as new vessels invade the non-vascular areas, the changes in the two series do no doubt approximate; but in the earlier stages we may distinguish between an ordinary inflammation and "inflammatio sine inflammatione."

The relative denseness and compactness of the tissues also introduce characteristic alterations: a dense tissue, such as bone, does not show the signs of reaction to injury to nearly the same extent as does a loose tissue — such as the omentum, for example — thus, in the former there may be a process almost as atypical as in non-vascular areas. The rigid framework of a tissue like bone prevents great vascular dilatation and exudation, but at the same time may be the seat of great pain due to pressure of the confined exudate upon the nerve endings. The loose connective tissue of a structure like the omentum, on the other hand, permits great exudation with little or no pain.

The influence of structure is well seen in comparing the course of inflammation affecting cutaneous, mucous and serous surfaces respectively. Where we have to deal with cutaneous surfaces, or surfaces formed of squamous epithelium, there the increased exudation, and the resistance offered by the layers of flattened cells to the free exit of the exuded fluid, lead towards the formation of vesicles or blisters. In the case of serous surfaces, which form the walls of a moist cavity, the irritant, affecting primarily but one portion of the surface, is very likely to be borne into the cavity with the exudate and to set up an inflammation

extending over a very large portion of the surface. Mucous and cutaneous surfaces, which are not thus the boundaries of cavities, exhibit a more marked disposition to the production of localised inflammation and of ulcers; the superficial layers indeed of a well-formed epithelium or mucous membrane, by the protective powers of their cells, form a defence against irritation from without: thus the superficial exudate from a region of local inflammation cannot easily produce a superficial extension of the process.

Not only the nature of the tissues, but their function also, profoundly affect the character of the inflammatory manifestation. Thus, excretory organs, by the very nature of their function, during the attempt to remove noxious substances from the system, are especially liable to generalised parenchymatous inflammations, — the irritation not being local, but affecting at the same time all the cells whose part it is to take up and excrete the irritant bodies.

B. The Position of Tissues. — It is difficult to consider the position and relationship of tissues as they affect the inflammatory manifestations, without continually touching upon their structure. Nevertheless, the two, though very closely connected, do not go hand in hand.

A familiar instance of modification in form brought about by position is to be seen in the result of suppurative inflammation — in the development of ulcerous conditions when the process affects free surfaces, of abscesses when it attacks deeper tissues. The process in the two cases is virtually the same: there is the same abundant determination of leucocytes, the same degeneration of them into pus. Yet apart from the gross difference in form, there are minor differences between the two. There is, for instance, relatively much more serous exudation from the free surface of an ulcer than there is into and around an abscess. As a general rule, inflamed tissues near a free surface are the seat of more abundant exudation. Of this liability for free surfaces to be the seat of serous inflammation I have already spoken. The skin, with its thick dermal layer, affords a good example: when the full suppurative stage is not reached, inflammation affecting the outermost layers of the derma is most often of a vesicular or œdematous character; when it affects the deeper layers of the derma the serous infiltration is less evident.

Yet another example of the influence of position in modifying form is seen in enteric fever. In this malady, the lymphoid tissue forming the Peyer's patches becomes the seat of excessive cellular infiltration and proliferation, undergoes necrosis, and is cast off, leaving the well-known ulcers. The lymphoid tissue of the neighbouring mesenteric gland likewise undergoes great infiltration and enlargement, but necrosis rarely implicates the whole of a gland: notwithstanding the previous extensive inflammation, the glands commonly recover their normal appearance and size.

Beyond this there are few broad principles to be laid down concerning the relationship between forms of inflammation and position that do not essentially depend upon the structure and functions of the tissues.

Much can be said concerning the intimate connection between position and liability to inflammation; but this and the allied and most important subject of the protective mechanisms of sundry tissues against injury are away from our present point.

C. The Relative Intensity of the Irritant is a more frequent and potent cause of variation. I have already in several places referred to the ratio between the resistant powers of cells and the intensity or virulence of the irritant as it affects the inflammatory process, and have shown how much that was previously vague has been made clear by bacteriological research; while, at the same time, it has brought home the truth that the various forms of inflammation merge insensibly one into the other.

Broadly speaking, it may be stated, as a result of these studies, that, *cæteris paribus*, increased virulence of any given microbe or diminished power of resistance on the part of the organism or of the tissues, leads to corresponding alterations in the phenomena of inflammation at the region of inoculation; and *vice versa*.

Thus, if a pathogenetic microbe, such as that of anthrax or erysipelas, be greatly attenuated, the effects of inoculation into the subcutaneous tissues may be scarcely recognisable. If the attenuation be not so extreme some hyperæmia, a determination of leucocytes, and, relatively, very little exudation, will be seen; and in the course of a day or two all traces of inflammation may have disappeared. With slightly more virulent microbes the migration of leucocytes may be followed by their breaking down and consequent abscess formation; with further increase of intensity of action the migration of leucocytes may be wanting, while the exudation extends and the inflammation rapidly spreads and leads to a septicæmia. A like series of changes is observable if the strength of virus be constant and animals more and more susceptible (or less and less refractory) be inoculated.

The variation in tubercular lesions, from isolated dense fibroid masses to loosely formed cell accumulations and diffuse tubercular inflammation, is evidently explicable on this law. The law holds good also, not merely for bacterial products, but for other irritants also. The effect of croton oil varies with the strength of the solution applied; and, as shown by Samuel, according to the condition of the animal. The same is true of abrin and other vegetable extracts.

Turning to physical irritants, while here the intensity of the irritant alone or almost alone is called into play, numerous examples can be given of the effects of variation in this one respect upon the inflammatory manifestation — effects of cold, for instance, varying from chilblain through inflammatory œdema to gangrene; of heat varying from hyperæmia through vesicular inflammation to complete destruction of tissue; and, again, effects of caustic substances. In this era of aseptic surgery we may forget what was well known to the last generation of surgeons, that caustic substances may be employed either to originate a benign and reparative inflammation (as in the case of indolent ulcers);

or, in larger quantities or greater intensity, to bring about a state in which the death of the tissue elements is far in excess of the subsequent repair. Thus then, according to the above-mentioned ratio, inflammation in a tissue may vary by insensible gradations from a mere hyperæmia up to a spreading suppurative or gangrenous process; and from a purely local manifestation to the development of what may be termed an inflammation of the whole organism.

D. The Nature of the Irritant. — It is clear, then, that it is impossible to base a classification upon the nature of the irritant: the attempt to mark off sharply the inflammations caused by mechanical and chemical noxæ from those produced by bacteria and their products must be given up. Hüter's proposition that suppuration can only be induced by microbes has been repeatedly shown to be erroneous. Thanks more especially to the researches of Councilman, Leber, Grawitz and de Bary and Straus (many more names might be mentioned in this connection), we now know that many chemical substances are capable of causing pus formation.[1] Among these may be mentioned turpentine, croton oil, mercury, copper and silver nitrate. On the other hand, although this pyogenetic property is not confined to microbes and their products, yet among microbes it is not the common property of all. Some, like the bacillus of tetanus, never in themselves induce pus formation: others, like the bacillus of tuberculosis, lead characteristically to tissue growth and the formation of inflammatory neoplasms rather than to pus formation. Even among those which, like the micrococci, are highly pyogenetic, the formation of abscesses only occurs when there is a definite relationship between the virulence of the microbe and the resistance of the organism. The reverse is equally true, that numerous microbes, not specially pyogenetic, produce pus under peculiar conditions. Thus, the bacillus of enteric fever, when it multiplies in the middle ear, induces a suppurative otitis, and, as Dr. C. F. Martin has shown, it is further capable of originating a suppurative arthritis.

In fact, under varying conditions the same microbe can induce very various forms of inflammation. Thus, Charrin has shown that the B. pyocyaneus and its products are capable of inducing in one organ — the kidney — pathological conditions so diverse as acute, chronic, parenchymatous, interstitial and thrombotic nephritis, with, in addition, cyst formation and amyloid degeneration.[2] This same microbe can induce acute suppuration in the anterior chamber of the eye; and when inoculated into the blood cause a hæmorrhagic inflammation of the serous surfaces. Hence we can proceed further and state that no strict classification of inflammation can be made according to the nature of the

[1] While this is so, it must be borne in mind that under ordinary conditions these substances very rarely act upon the organism in a state of sufficient concentration to be pyogenic. Thus, while it is impossible to make a sharp line of demarcation between bacterial and chemical irritants, it holds true in the main for man that suppurative disease is an indication of the presence and growth of microbes.

[2] These changes are comparable with the diverse conditions of the kidney in the human being brought about by the scarlatinal virus.

bacterial irritants: it is, however, possible to make a general grouping of those affecting man, as follows: —

(i.) Micro-organisms characteristically leading to pus and abscess formation — Staphylococci and streptococcus pyogenes, B. anthracis.

(ii.) Those leading to abundant exudation with necrosis — B. of malignant œdema.

(iii.) Those leading to cellular infiltration without usually causing abscess formation — B. typhi abdominalis, M. gonorrhœæ, B. diphtheriæ, etc.

(iv.) Those inducing characteristically the development of inflammatory neoplasms — B. tuberculosis, B. pseudo-tuberculosis, B. mallei, Actinomyces, Aspergillus fumigatus.

Similarly, chemical substances may roughly be grouped into —

(*a*) Substances causing so slight an irritation when introduced into the organism as to induce cellular overgrowth only in their immediate neighbourhood — such as bland foreign bodies, bullets, etc.; inhaled particles of coal, stone, iron, and the like, conveyed into the pulmonary lymphatics.

(*b*) Substances leading to vesicular inflammation, *e.g.* blistering agents, such as cantharides. (This result, however, depends more upon the position than the nature of irritant.)

(*c*) Substances leading to cell necrosis, followed by the formation of granulation tissue — caustic agents.

(*d*) Substances leading to cell necrosis and suppuration, such as copper, mercury, mineral acids, etc. (a very rare result in man).

These lists, from the considerations given above, are necessarily unsatisfactory and imperfect.

Other Considerations. — Among other factors varying the inflammatory process may be mentioned the duration of the action of the irritant, which of necessity must modify the extent of the manifestations of disturbance in the tissues. A simple aseptic incision, for example, leads to a much milder and slighter series of changes than do the prolonged presence and growth of the tubercle bacillus. Yet while at first it might appear an easy matter to name case after case where the irritant has but a momentary action, upon further consideration it is found that, in the majority of cases of purely mechanical injury, this is not the case; or, to express the matter more exactly, in the case of physical injuries, it is not the act of wounding that causes the inflammation, but the damage inflicted upon the cells of the tissues; as, to a very large extent, inflammation is set up by the products of the injured and destroyed cells. A bone may be suddenly broken, and nevertheless, even under the most favourable circumstances, pain, swelling, and congestion may affect the region of fracture for several days. One or other region of the body may be rapidly frozen: the inflammation does not manifest itself till after the physical agent has ceased to act, but it continues for hours, and even for days.

There are, moreover, physical irritants of another nature producing

definitely chronic inflammation; I refer to foreign bodies which have gained an entrance into the system. These if bland in themselves may nevertheless cause irritation. A good example of the extensive inflammation which such bodies may set up is seen in the dense fibrous interstitial tubercular masses developed in the lungs of stone-masons around fine silicious particles carried into the lymphatics from the alveoli.

From such examples it will be evident that no satisfactory distinctions between bacterial irritants on the one hand, and physical irritants on the other, can be founded on the duration of irritation. This factor plays no easily recognised part in determining the various forms of inflammation, and consequently I have forborne to place it in the list at the beginning of this chapter.

In thus passing rapidly over the influence of each of the four main causes of variation I have of necessity excluded sundry forms of inflammation due to the combined action of two or more. There are, for instance, such well-marked forms as the catarrhal and croupous, due to the interaction of all four factors: embolic inflammation and lymphangitis have also been passed over; these, however, are not so much forms of inflammation as inflammatory processes occurring in special regions as a result of special methods of conveyance of the irritants.

The factors then are so many, and their interaction so varied, that anything approaching to an orderly classification is hopeless. What I have here written must be regarded, not as an attempt to formulate such a classification, but as an attempt to indicate briefly how the nature and position of the tissues, and the nature and intensity of the irritant bring about modifications in the process of inflammation.

Chapter 2. — On Systemic Changes Consequent upon Inflammation

The results of an acute local inflammatory process are not confined to the immediate locality, but associated alterations in the system at large have long been recognised; yet while recognised these systemic changes have been but little studied: I cannot pass the matter over in silence, but my setting forth of it must necessarily be very brief and imperfect.

I cannot here say more upon the effect of local irritation on the nervous system than that, apart from direct reflex action leading to changes of nervous origin in the region of injury and the reflexes affecting associated regions, the higher centres, and through them the system at large, may become affected by paths that it is not always easy to trace.

The disturbances of the nervous system which accompany local injury can be but vaguely and indefinitely described. As regards the secondary effects, the recent most suggestive work of Prof. Roy and Dr. Cobbett upon *Shock* [*vide* art. on "Shock" in a later volume] indicates that there is here a rich field for yet further research. Of the changes in the general circulation, and more especially in the circulating blood, thanks to the

observations of Von Limbeck, Rieder, Löwitz, and Sherrington, we are in possession of more exact knowledge. On acute local inflammation of some extent the circulating blood becomes inspissated; by exudation it loses some of its plasma, while the more solid constituents — the red corpuscles — do not escape. The amount of fluid lost to the circulation is not equalised by increased entrance of lymph into the circulation: in one experiment of Prof. Sherrington the blood remained apoplasmic (*i.e.* its specific gravity remained heightened) for more than sixty hours after the infliction of injury. This apoplasmia or diminution in the relative amount of plasma in the blood appears to depend in some measure upon the extent of the vascular area involved in the inflammation; for example, Sherrington shows that when both feet are involved, by plunging the limbs in water of 52° C., the apoplasmia is more severe than in experiments affecting one foot only. Another well-marked change in the blood concerns the leucocytes. As suspected by Löwitz and proved by Sherrington, there is, in some forms of inflammation at least, a primary diminution in the number of leucocytes per unit volume of blood (leucocytopenia), followed by a marked increase in the number of leucocytes in the blood (leucocytosis). The number of leucocytes was in some instances increased sevenfold. In the leucocytopenia of inflammation, the diminution is chiefly confined to the finely granular leucocytes — the finely granular oxyphile cells of Kanthack and Hardy. These observations of Sherrington are confirmed by the observations of Everard, Demoor, and Massart.

Whether the diminution be due to disintegration, or to collection in some area of the circulation, is not yet determined. The leucocytosis may become obvious within an hour after the establishment of a local lesion; and it may be prolonged for several days, even in cases where the injury has been of a mechanical nature. Here, again, according to most observers, it is chiefly the polynuclear or finely granular oxyphile cells which increase in numbers. It is interesting to note that coincidently the coarsely granular eosinophile cells appear to undergo great diminution. I can do no more than point out the existence of those blood changes, and further that changes in the number of leucocytes in the blood are certainly not accounted for by the number passing from the blood into the inflamed area. It would seem that local inflammation in some way brings about an over-stimulation of lymph glands, whereby an increased number of leucocytes are poured into the blood; or it may initiate increased proliferation of the leucocytes already in the circulation; but how one or other of these effects is produced is at present unknown. Certainly the direct introduction of the products of bacterial growth into the circulating blood may lead to a more or less pronounced and rapid diminution of the number of leucocytes in the blood, and this diminution, as shown by Löwitz, may be preliminary to a subsequent increase.

The further important general disturbance associated with local injury, more especially when of bacterial origin, namely, the occurrence of fever, will be described in another article. Bacteriological studies

lead to the conclusion that traumatic fever, at any rate, is largely due to the diffusion in the blood stream of soluble bacterial products, and of the products of tissue destruction derived from the inflammatory focus.

Chapter 3. — Conclusion

In studying thus the reactions of the organism to injury, we are impressed by the multifariousness of natural processes; the end may be attained not in one way only but in many. "It is not by cells of one order alone — by phagocytes — or by leucocytes in general and only leucocytes, or merely by the reaction on the part of the fixed cells of the tissue, or by vascular changes alone, or by altered temperature, or solely by the chemical and mechanical action of the exudate that repair is effected. All means are employed to antagonise the irritant and to effect healing. The cells of the body, fixed and free, play their part; the nervous system aids the process; the bodily humours render efficient help; modifications in the vessel walls and blood stream are valuable auxiliaries. Diverse processes are employed, now one more particularly, now another, according to the needs of the moment, but none exclusively."

The time has come when, example after example having clearly indicated the meaning and the tendency of that response, we may securely acknowledge the tendency, and see in inflammation not merely the response to injury, but the attempt to repair injury. To object that a definition containing this statement is teleological is absurd in the face of fact after fact that can be interpreted on this assumption only. What is the development of cicatricial tissue but an attempt at repair? What other meaning can be ascribed to the increased bactericidal power of the inflammatory exudate as compared with that of ordinary lymph and blood serum? Why do leucocytes accumulate in a region of injury? Why do some of them incorporate bacteria and irritant particles, and others bring about the destruction of these without necessarily ingesting them? All these are means whereby irritants are antagonised or removed, and reparation and return to the normal sought after.

It must be kept in mind that attempt to repair may be far from repair. Indeed, we frequently find that the reaction to injury is disproportionate to the strength of the irritant, being either insufficient or excessive. The exudation may possess but slight bactericidal powers, or may be poured out in such quantities that the microbic irritant, instead of being retained in the region of injury, is conveyed outside that region; the wandering cells instead of destroying, may undergo destruction; they may incorporate bacteria, but not be able to annihilate them; the fixed cells may either form an incomplete cicatrix, or continue to proliferate in excess. The means of defence on the part of the organism are not so much a preparation in advance as an inheritance or an acquirement — either a transmission from those forms which, being possessed of the most highly developed means of defence, have survived while forms with fewer resources have been destroyed; or, on the other hand, an accession derived

from previous successful resistance: not being a preparation in advance, the reaction to injury is not exactly proportionate to any and every irritant.

But the mere statement that inflammation is an attempt to repair injury, or that it is the response thereto, is insufficient as a definition, for thereby the general disturbances which may accompany the changes occurring at the seat of lesion are included; these, however, may be excluded without seriously affecting our conception of the process, in fact with positive advantage to a clear comprehension of the distinction between inflammation and fever. And, further, if what I have urged in the chapter upon the part played by the nervous system be correct, account must be taken of the fact that the leading phenomena associated with the inflammatory process may occasionally present themselves solely under the direction of perverted nerve action, and apart from actual local injury.

Hence I am inclined to consider that we can now pass beyond the conception of the process with which I began this article, and cannot merely regard it as a succession of changes in a part constituting the reaction to injury, but can with propriety acknowledge the purpose of that succession. From these considerations I am led to define inflammation *as the series of changes constituting the local manifestation of the attempt at repair of actual or referred injury to a part, or, briefly, as the local attempt at repair of actual or referred injury.*

So diverse are the opinions of pathologists upon many branches of this subject of inflammation, and so great is the amount of recent research that I can neither hope that all the conclusions here set down will gain acceptance, nor that in these pages, inevitably condensed as they are, I have succeeded in recognising and duly acknowledging all work of primary importance. It is possible also that, having been unavoidably prevented of late from seeing and discussing with others the results they have obtained, I may in some cases have viewed facts in a wrong perspective. In the rapid progress of our science, much, it may be, that is here set forth will be modified. Nevertheless I hold that the conception of the inflammatory process indicated in this article is that which embraces the largest number of like phenomena, and excludes most satisfactorily those which if associated are unessential; and that it is by the study of cellular pathology in its strictest sense that the surest advance has been and is to be made in our knowledge of this the dominating process in disease.

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SELECT BIBLIOGRAPHY

I. OF INFLAMMATION IN GENERAL

1. BENNET. *On Inflammation.* Edinburgh, 1844. — 2. BILLROTH. *Wiener klin. Wochenschr.* 1892. Nos. 1 and 2. — 3. BOUCHARD. *Semaine méd.* 1891. No. 20. — 4. BURDON-SANDERSON. *Holmes's System of Surgery*, i. (gives extensive select bibliography). — 5. BURDON-SANDERSON. Croonian Lectures, 1892. *Vide Lancet*, ii. 1892, pp. 1027, 1083, 1149, and 1207. — 6. COHNHEIM. *Vorlesungen*, second edition. Leipzig, 1882. Translated by Dr. A. B. M'Kee, New Sydenham Society, 1889. –

7. Cornil et Ranvier. *Manuel d'Histologie pathologique*, i. — 8. Councilman. *Dennis's System of Surgery*, i. 1895. — 9. Hamilton. *Text-book of Pathology*, i. 1889 (gives extensive bibliography). — 10. Hüter. *Grundriss der Chirurgie*, i. 1883. — 11. Koch. *Wundinfectionskrankheiten*. Leipzig, 1878. — 12. Leber. *Die Entstehung der Entzündung*. Leipzig, Engelmann, 1891. — 13. Letulle. *L'Inflammation*. Paris, 1893. — 14. Metschnikoff. *Pathologie comparée de l'Inflammation*. Paris, Masson, 1892. Eng. transl., London, 1894. — 15. Neumann. "Uber dem Entzündungsbegriff," *Ziegler's Beitr.* v. 1889, p. 347. — 16. Recklinghausen. *Handbh. d. allgem. Path.* 1883. — 17. Roser. *Entzündung und Heilung*. Leipzig, 1886. — 18. Samuel. *Virch. Arch.* lv. 1872, p. 380. — 19. Samuel. *Die Entzündungsprocess*, 1873. — 20. Thoma. "Ueber Entzündung," *Berlin klin. Wochenschr.*, 1886 (on the suppression of the term "Inflammation"). — 21. Virchow. *Cellular Pathology*. Eng. transl. from second edition by Chance. London, 1860. — 22. Wagner. *Hdbuch. der allgem. Path.* Eng. translation, New York, W. Wood, 1879 (gives older literature very fully). — 23. Weigert. "Entzündung," *Eulenburg's Realencyclopädie*, 1880, iv. p. 644. — 24. Ziegler. *Lehrbuch der allgemeinen pathologische Anatomie*. 8th German edition, 1894. — 25. Ziegler. *Rede gehalten am 25 April 1892 zur akademischen Feier*. Freiburg, Lehmann, 1892.

II. The Comparative Pathology of Inflammation

26. Greenwood, Miss M. — *J. of Physiol.* vii. 1886, p. 254; viii. 1887, p. 263; xi. 1890, p. 576; xvi. 1894, p. 441. — 27. *Proc. Roy. Soc.* liv. 1893, p. 466, "Intercellular Digestion." — 28. Hardy. *J. of Physiol.* xiii. 1892, p. 165, "Blood Corpuscles of Crustacea." — 29. Krukenberg. *Unters. a. d. physiol. Inst. in Heidelberg*, ii. 1878, p. 273, "Intercellular Digestion." — 30. Le Dantec. *Ann. de l'Inst. Pasteur*, iv. 1890, p. 776, and v. 1891, p. 163. — 31. Loeb. *Biol. Lectures, Marine Biol. Lap., Wood's Hole*, 1893. Boston, Ginn and Co., 1894, p. 43. — 32. Metschnikoff. *A. de l'Inst. P.* iii. 1889, and No. 14, gives main literature. — 33. Pfeffer. *Unters. a. d. botan. Inst. in Tübingen*, vols. i. and ii. — 34. Reinke. *Unters. a. d. bot. Inst. in Göttingen*, 1881. — 35. Stahl. *Botan. Zeitung*, 1884, Nos. 10–12.

III. The Steps of the Inflammatory Process in the Higher Animals

In addition to Nos. 6, 7, 8, 12, 19 and 23, consult — 36. Flemming. *Virch. Arch.* lvi. 1872, p. 146, on "Development of Fibrin in Inflamed Tissues." — 37. Hess. *Virch. Arch.* cix. 1887, p. 365. — 38. Hohnfeldt. *Ziegler's Beitr.* iii. 1888, p. 343. — 39. Jacobs. *Beitr. z. Histol. d. acut. Entzündung d. Cornea*, Inaug. Diss. Bonn, 1887. — 40. Ranvier. *Ctes. rend. d. l'Acad. d. Sc.* 1891, April 20th, p. 845. — 41. Senftleben. *Virch. Arch.* lxxii. p. 542. — A satisfactory bibliography of this subject is given by Burdon-Sanderson, Nos. 4 and 5. For full references to recent work upon mycotic inflammation consult Baumgarten's *Jahresbericht*.

IV. On the Forms and Varieties of Leucocytes

42. Ehrlich. "Farbenanalytische Unters. z. Histol. u. Klinik des Blutes," *Gesamm. Mitthl.* Berlin, Hirschwald, 1891. — 43. Everard, Demoor, and Massart. *A. de l'I. P.* vii. 1893. — 44. Gluge. *Observat. nonn. microscop. in Inflamm.* 1835. — 45. Gulland. *Lab. Rep. R. C. P. Edin.* iii. 1891, p. 106. — 46. Gulland. *J. of Pathol.* ii. 1894, p. 447. — 47. Wharton Jones. *Phil. Trans.* 1846, p. 64. — 48. Kanthack. *Med. Chron.* New series, i. 1894, pp. 246, 332. — 49. Kanthack and Hardy. *J. of Pathol.* xvii. 1894, p. 81; and *Phil. Trans.* 1894. — 50. Mesnil. *A. de l'I. P.* ix. 1895, May. — 51. Metschnikoff. *B. M. J.* 31st Jan. 1891, and No. 14. — 52. Ranvier. "Des Clasmatocytes," *Ctes. rend. d. l'Acad. des Sc.* cx. 1889, p. 165. — 53. Rieder. *Beitr. z. Kenntniss d. Leucocytose*, Leipzig, 1892; and *Atlas d. klin. Microscopie des Blutes*. Leipzig, 1892. — 54. Rindfleisch. *Pathol. Histologie*, 1861; und *Exptelle. Studien ü. d. Histologie des Blutes*. Leipzig, 1863. — 55. Max Schultze. *Arch. f. mikr. Anat.* i. 1863, p. 1. — 56. Sherrington. *Proc. Roy. Soc.* lv. 1893, p. 161. — 57. Siawcillo. *A. de l'I. P.* ix. May 1895. — For fuller bibliography consult Nos. 46, 48, and 53.

V. On the Nature of Giant Cells

58. Borrel. *A. de l'Inst. Pasteur*, vii. 1893, p. 593. — 59. Duenschmann. *J. of Pathol.* iii. 1894, p. 118. — 60. Faber, Knud. *J. of Pathol.* i. 1893, p. 349. — 61. Koch. *Mittheil. a. d. kaiserl. Gesundheitsamt*, ii. 1884. — 62. Langhans. *Virch. Arch.* xlii. 1868, p. 382, and xlix. 1870, p. 66. — 63. Marchand, P. *Virch. Arch.* xciii. 1883. — 64. Johannes Müller. *Ueber den feineren Bau und die Formen der Krankhaften-Geschwülste.* Berlin, 1838. — 65. Ribbert. *Der untergang. pathogen. Schimmelpilze im Körper.* Bonn, 1887. — 66. Ruffer. *A. de l'Inst. P.* v. 1891. — 67. Soudakewitch. *Virch. Arch.* cxv. 1889. — 68. Stchastny. *A. de l'Inst. P.* v. 1891, p. 225. — 69. Virchow. *Virch. Arch.* xiv. 1858, p. 47. — 70. Weigert. *D. med. Wochenschr.* 1885, and *Virch. Arch.* cxiii. 1889. — 71. Ziegler. *Expt. Untersuch. ü. d. Herkunft d. Tuberkelelemente.* Wurzburg, 1875. — Earlier literature given by Marchand (No. 63), later by Faber (No. 60).

VI. On Chemiotaxis

72. Councilman. *Virch. Arch.* xcii. 1883. — 73. Gabritchewski. *A. de l'I. P.* iv. 1890, p. 346. — 74. Kanthack. See No. 48, and *B. M. J.*, June 18th, 1892. — 75. Leber. See No. 12. — 76. Massart, J. *A. de l'I. P.* vi. 1892, p. 321. — 77. Massart and Bordet. *J. d. l. Soc. Roy. d. Sc. Med. et Nat. de Bruxelles*, 1890. — 78. Massart and Bordet. *A. de l'I. P.* v. 1891, p. 417. — 79. Pekelharing. *La Semaine méd.* 1889, No. 22, p. 184. — 80. Pfeiffer. See No. 33. — 81. Stahl. See No. 35. — For fuller bibliography consult Massart and Bordet, No. 77.

VII. On Phagocytosis — General Articles

82. Adami. *Med. Chron.* Nov. and Dec. 1891. — 83. Baumgarten. *Ctbl. f. klin. Med.* 1888, No. 26; *Zeigler's Beitr.* vii. 1889; *Berl. klin. Woch.* 1884, Nos. 50 and 51. — 84. Bitter. *Zeitschr. f. Hygiene*, iv. 1888, p. 405. — 85. Discussion on Immunity (Roux, Metschnikoff, Hankin, Behring, Buchner, etc.). *Trans. Internat. Congr. of Hygiene, London*, 1891, vol. ii. — 86. Discussion on Immunity. *Internat. Congr. of Hygiene Buda-Pesth*, 1894 (Metschnikoff, Roux, Buchner, Denys, etc.), *Ctbl. f. Bakt.* 1894. — 87. Discussion on Immunity. *Path. Soc. London*, 1892 (Woodhead, Klein, Hankin, Martin, etc.); *Path. Trans.* 1892, v.; also *B. M. J.* of Feb. 20 and 27, 1892. — 88. Lubarsch. *Fortschr. d. Med.* viii. 1890, No. 17. — 89. Lubarsch. *Zeitschr. f. klin. Med.* xviii. 1891, p. 421. — 90. Metschnikoff. See Nos. 14 and 51. — 91. Nieczajeff. *Verhandl. das X. Internat. Med. Congress, Berlin*, 1890, ii. pt. 3, p. 54. — 92. Sanarelli. *Ctbl. f. Bakt.* x. 1891, p. 514. — 93. Sternberg. *Am. J. of Med. Sc.* April 1881. — For the abundant literature on this subject consult Bitter (No. 84) and Lubarsch (No. 88), as also the full bibliography (up to 1892) given by Sternberg in his *Manual of Bacteriology*. New York, 1892, and (to 1895) in his *Immunity, Protective Inoculation, etc.* New York, 1895.

VIII. Phagocytosis in Connection with Pathogenic Microbes of Various Diseases (for Shortness Names of Diseases alone given)

Actinomycosis: — 94. Marchand. *Eulenburg's Realencyclopädie*, article "Actinomycosis." — 95. Boström. *Zeigler's Beitr.* ix. 1890. — 96. Pawlowsky and Maksukoff. *A. de l'Inst. Pasteur*, vii. 1893, p. 544. **Anthrax**: — 97. Hess. *Virch. Arch.* cix. p. 365. — 98. Koch. *Cohn's Beitr. z. Biol. der Pflanzen*, ii. 1876. — 99. Lubarsch. *Fortschr. d. Med.* 1888, p. 4. — 100. Metschnikoff. *Virch. Arch.* xcvii. p. 502, and *A. de l'Inst. Pasteur*, i. 1887, p. 7. — 101. Nutall. *Zeitschr. f. Hygiene*, iv. 1888. — 102. Petruschky. *Zeigler's Beitr.* iii. 1888, p. 357, and *Fortschr. d. Med.* viii. 1890, No. 15. **Cholera**: — 103. Metschnikoff. *A. de l'I. P.* viii. 1894, p. 529. — 104. Pfeiffer and Wasserman. *Zeitschr. f. Hygiene*, xiv. 1893, p. 59. — 105. Cantacuzene. *Récherches sur le mode de destruction du Vibrion Cholerique.* Paris, 1894. **Diphtheria**: — 106. Gabritchewski. *A. de l'I. P.* viii. 1894. — 107. Massart. See No. 76. **Erysipelas**: — 108. Metschnikoff. *Virch. Arch.* cvii. 1887, p. 209, and numerous other observers. **Gonorrhœa**: — 109. Neisser and all subse-

quent observers (for bibliography see Sternberg). **Hog Cholera**: — 110. METSCHNIKOFF. *A. de l'I. P.* vi. 1892, p. 289. **Leprosy**: — 111. METSCHNIKOFF and SOUDAKEWITCH. *Virch. Arch.* cvii. 1887, p. 228 (and all recent observers). **Malaria**: — 112. GOLGI. *Gaz. degli Ospitali*, 1886, No. 53 (parasites in leucocytes, as distinguished from red corpuscles). **Mouse Septicæmia**: — 113. METSCHNIKOFF. *A. de l'Inst. P.* v. 1891. **Pathogenetic Torulæ in Daphnia**: — 114. METSCHNIKOFF. *Virch. Arch.* xcvi. **Pathogenic Moulds (Aspergillus, etc.)**: — 115. RIBBERT. See No. 65. **Pneumonia (Diplococcus)**: — 116. GAMALEIA. *A. de l'I. P.* ii. 1888, p. 445. — 117. ISAEFF. *Ibid.* vii. 1893, p. 260. — 118. TCHISTOVITCH. *Ibid.* iii. 1889, p. 337. **Relapsing Fever**: — 119. METSCHNIKOFF. *Ibid.* i. 1887, p. 329. — 120. SOUDAKEWITCH. *Ibid.* v. 1891, p. 545. **Suppuration (Staphylococcus pyogenes)**: — 121. FLECK. *Die acute Entzündung der Lunge.* Dissert., Bonn, 1886. — 122. HESS. See No. 37. — 123. HOHNFELDT. See No. 38. — 124. LAHR. *Ueber d. Untergang d. Staph. in der Lunge.* Dissert., Bonn, 1887 (and numerous other observers). **Swine Erysipelas** ("Rouget" or "Rothlauf"): — 125. METSCHNIKOFF. *A. de l'I. P.* iii. 1889, p. 289. — 126. SCHÜTZ. *Arb. a. d. Kaiserl. Gesundheitsamt*, i. 1885, p. 61. — 127. TCHISTOVITCH. See No. 118. **Symptomatic Anthrax (Quarter-evil)**: — 128. RUFFER. *B. M. J.* May 24th, 1890. — 129. RUFFER. *A. de l'I. P.* v. 1891, p. 673. **Tuberculosis**: — 130. BORREL. See No. 58. — 131. METSCHNIKOFF. See No. 51. — 132. STSCHASTNY. *Virch. Arch.* cxv. 1889, and No. 68. **Vibrio Gamaleia vel Metschnikovi**: — 133. METSCHNIKOFF. *A. de l'I. Pasteur*, v. 1891, p. 465. — 134. SANARELLI. *Ibid.* vii. p. 225.

IX. On the Bactericidal Action of the Bodily Humours

135. BEHRING and NISSEN. *Zeitschr. f. Hygiene*, viii. 1890, p. 424. — 136. BUCHNER. *Arch. f. Hygiene*, x. 1890, pts. 1 and 2; *Centrlbl. f. Bakt.* v. 1889, p. 817, and vi. p. 1. — 137. EMMERICH and DI MATTEI. *Fortschr. de Med.* vi. p. 729. — 138. VON FODOR. *D. Med. Woch.* 1887, p. 745; and *Ctbl. f. Bakt.* vii. 1890, p. 753. — 139. HANKIN. See No. 150. — 140. LUBARSCH. *Ctbl. f. Bakt.* vi. 1889, p. 841. — 141. NISSEN. *Zeitschr. f. Hygiene*, vi. 1889, p. 487. — 142. NUTTALL. *Ibid.* iv. 1888, p. 353. — 143. PEKELHARING. *La Sem. méd.* 1892, p. 503. — 144. TRAUBE and GSCHLEIDEN. *Jahresbr. d. Schlesischen Gesell.* lii. 1874, p. 179. — 145. WEIGERT. *Fortschr. d. Med.* v. 1887, p. 733. — For other articles consult the works of Sternberg previously mentioned.

X. Upon Extra-Cellular Activity and the Production of Bactericidal and Toxicidal Substances from Wandering Cells, etc.

146. ADAMI. See No. 82. — 147. BUCHNER. *Fortschr. d. Med.* x. 1892, Nos. 9 and 10; *Münch. Med. Woch.* 1894; *Ctbl. f. Bakt.* xvi. 1894, p. 738, and No. 86. — 148. DENYS. *La Cellule*, 1894. — 149. DENYS and HAVEL. *Arch. de méd. exptle.* vi. 1894. — 150. HANKIN. *Proc. Roy. Soc.* xlviii. 1890, p. 93; *Ctbl. f. Bakt.* ix. 1892, p. 722; *Ibid.* vols. xi. and xii.; see also No. 85. — 151. KANTHACK and HARDY. *Proc. Roy. Soc.* Nov. 1, 1892. — 152. KANTHACK and HARDY. *J. of Physiol.* 1893. — 153. KANTHACK and HARDY. *Phil. Trans.* 1894. — 154. KOSSEL. *Zeitschr. f. Hygiene*, xvi. 1894. — 155. METSCHNIKOFF. *A. de l'I. P.* viii. 1894, p. 706. — 156. PFEIFFER. *Zeitschr. f. Hygiene*, xvi. 1894, p. 268, and xviii. p. 1. — 157. RIBBERT. See No. 65. — 158. TIZZONI and CATTANI. *Berl. klin. Wochenschr.* 3. 1894. — 159. VAUGHAN and M'CLINTOCK. *Med. News* (N. Y.), Dec. 23rd, 1893.

XI. On the Part played by the Blood Vessels in Inflammation

In addition to COHNHEIM (No. 6), HAMILTON (No. 9), LEBER (No. 12), RECKLINGHAUSEN (No. 16), SAMUEL (No. 18), WEIGERT (No. 23), and ZIEGLER (No. 24), consult — 160. ARNOLD. *Virch. Arch.* liv. 1871, on "Development of Capillaries." — 161. CHARRIN and GLEY. *Arch. de Physiol.* Oct. 1890. — 162. ISRAEL. *Lehrbuch d. Path. Anat.* — 163. SAMUEL. *Virch. Arch.* xliii. 1868, p. 552, and li. 1870, p. 178 ("Change in Vessel Wall, inducing slowing of Current"). — 164. THIERSCH. *Pitha and Billroth's Chirurgie*, 1867, i. pt. 2, p. 529 (on "New Formation of Vessels"). — Fuller references given in ZIEGLER (No. 24) and HAMILTON (No. 9).

XII. On the Diapedesis of Leucocytes

165. Addison. *Exptl. and Pract. Researches upon Infl.* London, 1843.—166. Arnold. *Virch. Arch.* lviii. 1872, lxvi. 1874, and lxviii. 1875.—167. Binz. *Virch. Arch.* lix., lxxiii., and lxxxix.; *Arch. f. expt. Path.* vii. and xiii.—168. Cohnheim. See No. 6.—169. Disselhorst. *Virch. Arch.* cxiii. 1888, p. 108.—170. Hering. *Wien. Acad. Bericht.* lvii. 1868, p. 170 (on the "Adhesion of Corpuscles").—171. Kaltenbrunner. *Exp. circa stat. sanguinis et vasorum in infl.* 1826.—172. Kerner. *Pflüger's Archiv*, vii.—173. Lavdowsky. *Virch. Arch.* xcvii.—174. Metschnikoff. See No. 14.—175. Pekelharing. *Virch. Arch.* ci. 1885.—176. Recklinghausen. *Stricker's Handb.* Article, "Das Lymphgefässsystem."—177. Schklarewsky. *Pflüger's Arch.* i. 1868, pp. 603 and 657.—178. Thoma. *Berl. klin. Woch.* 1886.—179. Waller. *Phil. Mag.* xxix. 1846, pp. 217, 298, 397.

(α) On the Effect of Intra and Extra-Vascular "Toxins" upon Diapedesis

180. Bouchard. *Essai d'une théorie de l'infection. Verhandl. d. X. Internat. Med. Congr. Berlin*, 1890.—181. Charrin. *Ibid.* ii. pt. 3, p. 29.—182. Roger. *Contrib. à l'étude de l'immun. acquise*, p. 1.—183. Ruffer. *A. de l'I. P.* v. 1891, p. 673.—The earlier literature of diapedesis is given in detail by Wagner (No. 22) and Hamilton (No. 9). The last (German) edition of Ziegler (No. 24) is also very full.

XIII. On the Part played by the Nervous System in Inflammation

184. Berkley. *Anat. Anz.* viii. 1893, Nos. 23 and 24, and ix. 1893, Nos. 1 and 2; *Journ. of Comp. Neurol.* iii. 1893, p. 107; Pathol. Studies, Johns Hopkins Univ., *Neurology*, ii. 1894 ("Upon Nerve Endings in Vessel Walls, etc.").—185. Charcot. *Leçons sur les maladies du syst. nerveux.* Paris, 1873, p. 106.—186. Cohnheim. See No. 6.—187. Dache and Malvoz. *A. de l'I. P.* vi. 1892, p. 538 (on "Influence of Nervous System in Mycotic Inflammations").—188. De Paolis. *Riforma Medica*, 1889, No. 200.—189. Frenkel. *Arch. d. méd. expt.* iv. 1892, p. 638.—190. Gergens. *Pflüger's Arch.* xiii. p. 591.—191. Klebs. *Allg. Pathol.* ii. 1889, p. 384.—192. Lenhossek. *Arch. f. mikr. Anat.* xxxix. 1892 (on "Nerve Endings").—193. Mitchell, S. Weir. *Injuries of Nerves.* Phila. 1872, p. 168.—194. Ochotine. *Arch. de méd. expt.* iv. 1892, p. 245.—195. Retzius. *Biol. Untersuchungen*, Neue Folge, iii. 1891, p. 49, and iv.—196. Roger. *Comptes Rend. Soc. de Biol.* 3rd May 1890, and 22nd Nov. 1890.—197. Rütimeyer. *Arch. f. expt. Pathol.* xiv. p. 384.—198. Samuel. *Virch. Arch.* cxxi.—199. Saviotti. *Virch. Arch.* l. 1870, p. 592 (on "Dilation and Contraction of Arteries according to Nature of Irritant").—200. Severini. *La contrattilita dei capillari*, 1881.—201. Wagner, A. *Arch. f. klin. Chirurg.* xi. 1869, p. 1.

XIV. On the Part played by the Connective Tissue Cells in Inflammation

202. Arnold. *Arch. f. Mikr. Anat.* xxx. 1887.—203. Baumgarten. *Virch. Arch.* lxxviii. 1879; *Ueber Tuberkel und Tuberkulose*, i. *Die Histogenese des Tuberkulosenprocesses.* Berlin, 1885.—204. Borrel. See No. 58.—205. Coen. *Ziegler's Beitr.* ii. 1887.—206. Cornil and Ranvier. See No. 7.—207. Discussion at the Tenth Internat. Med. Cong. Berlin, 1890. (Ziegler, Marchand, Grawitz.) *Verhandl.* ii. pt. 3, p. 1.—208. Fischer. *Untersuch. ü. die Heilung von Schnittwunden der Haut.* Inaug. Diss. Tubingen, 1888.—209. Flemming. *Virch. Arch.* lvi. 1872, p. 146.—210. Grawitz. *D. Med. Wochenschr.* 1889. No. 23, on "Slumbering Cells."—211. Grawitz. *Virch. Arch.* cxviii. 1889.—212. Griffith, J. *J. of Pathol.* ii. 1894 (on "Development of Wandering from Fixed Cells").—213. Gull and Sutton. *Med.-Chir. Trans.* lv. 1872, p. 273.—214. Huchard. *Traité des maladies du cœur.* Paris, 1889 (on "Dystrophic Sclerosis").—215. Krafft. *Ziegl. Beitr.* i. 1884.—216. Marchand. *Ibid.* iv. 1888.—217. Metschnikoff. *Biol. Centrbl.* 1883, p. 561; *A. de l'I. P.* vi. 1892, p. 1 (on "Development of Wandering from Fixed Cells").—218. Nikiforoff. *Ziegl. Beitr.* viii. 1890, p. 419.—219. Podwyssozki. *Ibid.* i. 1884,

and ii. 1886. — 220. RANVIER. *Comptes rend. de l'Acad. d. Sc.* 1891, p. 843. — 221. REINKE. *Ziegl. Beitr.* v. 1889. — 222. ROY and ADAMI. *B. M. J.* 15th Dec. 1888. — 223. SCHELTEMA. *D. Med. Woch.* 1887, p. 463. — 224. SHERRINGTON and BALLANCE. *J. of Physiol.* 1889, p. 856. — 225. SOUDAKEWITCH. *A. de l'I. P.* vi. 1892, p. 13. — 226. STRICKER. *Studien a. d. Inst. f. exp. Pathol.* Vienna, i. 1870. — 227. TOUPET. *Des modifications cellul. dans l'infl. simple du peritoine.* Thesis, Paris, 1887. — 228. ZIEGLER. *Exp. Untersuch. ü. die Herkunft der Tuberkelelement.* Wurzburg, 1875. — 229. ZIEGLER. *Untersuch. ü. pathol. Bindgewebs- und Gefässneubildung.* Wurzburg, 1876. — 230. GRAWITZ, No. 211, gives a very full bibliography up to 1889 of the part played by the connective tissue cells. Consult also VIRCHOW (No. 21), COHNHEIM (6), METSCHNIKOFF (14), and ZIEGLER (24). The later German editions of *Ziegler's Handbook* contain a very judicial discussion of the relationship of fibrous hyperplasia to inflammation.

XV. On the Temperature Changes in Inflamed Areas

231. BILLROTH and HUFSCHMIDT. *Arch. f. klin. Chirurg.* vi. 1864, p. 373. — 232. HUNTER, JOHN. *On the Blood, Inflammation, and Gunshot Wounds.* London, 1793. — 233. HUPPERT. *Arch. d. Heilkunde,* xiv. 1873, p. 73. — 234. JACOBSON and BERNHARDT. *Med. Centlbl.* 1869, No. 19. — 235. LAUDIEN. *Ibid.* 1869, No. 19. — 236. SCHNEIDER. *Ibid.* 1870, No. 34. — 237. SIMON. *Holmes's System of Surgery,* 1860, article "Inflammation." — 238. WEBER, O. *Deutsch. Klin.* 1864, Nos. 43 and 44.

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